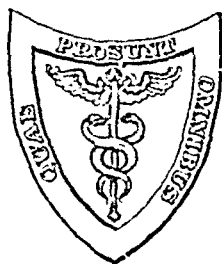


THE
AMERICAN JOURNAL
OF THE
MEDICAL SCIENCES

EDITED BY
JOHN H. MUSSER, JR., M.D.
E. B. KRUMBHAAR, M.D.
ASSOCIATE EDITOR

NEW SERIES

VOL. CLXVIII



LEA & FEBIGER
PHILADELPHIA AND NEW YORK
1924

COPYRIGHT
LEA & FEBIGER
1924

CONTENTS OF VOL. CLXVIII

ORIGINAL ARTICLES

The Surgery of Pulmonary Tuberculosis. By JOHN ALEXANDER, M.A., B.S., M.D.	1
The Use of Radium Radiations in the Treatment of Tonsils: A Further Report. By FRANCIS H. WILLIAMS, M.D.	18
Lipoids in 1000 Diabetic Bloods, with Special Regard to Prognosis. By H. GRAY, M.D.	35
Splenectomy, Its End-results and Clinical Indications. By RALPH C. LARRABEE, M.D.	47
Studies in Cholelithiasis (IV. The Late and Permanent Results of the Various Types of Operation on the Biliary Passages with Especial Reference to the Cholesterol Metabolism). By ABRAHAM O. WILENSKY, M.D., and MARCUS A. ROTHSCHILD, M.D.	66
The Use of Sulphur in the Treatment of Arthritis Deformans. By HOBART A. REIMANN, M.D., and GEORGE W. PUCHER, PH.D.	77
Sulphemoglobinemia; with Report of a Case Having a Definite Etiology. By KARL VOGEL, M.D.	89
The Value of Alkali in Dye Therapy. By VICTOR BURKE, PH.D., and IRENE GRIEVE, B.S.	98
The Hematological Responses to Injections of Streptococci. By LOTIS A. JULIANELLE, M.S., PH.D.	115
The Use of Tryparsamide in Neurosyphilis. By W. F. LORENZ, M.D., A. S. LOEVENHART, M.D., THOMAS F. REITZ, M.D., and C. P. ECK, M.D.	157
Arteriosclerosis: An Analysis of Eighty-six Necropsies. By FRED- WILLIUS, M.D., and GEORGE, E. BROWN, M.D.	165
Arterial Occlusion: A Perfectly Definite Symptom-complex: Report of Thirteen Cases with One Autopsy. By HERMON C. M.D.	181

A Comparative Study in Digifolin Administration. By NORMAN E. CLARKE, M.D.	201
The Effect on the Blood of Irradiation, Especially Short Wave Length Roentgen-ray Therapy. By GEORGE R. MINOT, M.D., and ROY G. SPURLING, M.D.	215
Primary Carcinoma of the Liver. By B. M. FRIED, M.D.	241
The Surgery of Pulmonary Tuberculosis. By JOHN ALEXANDER, M.A., B.S., M.D.	268
The Cause of Death in Diabetes Mellitus. By REGINALD FITZ, M.D., and WM. P. MURPHY, M.D.	313
The Occurrence of Herpes Zoster in Hodgkin's Disease. By HENRY K. PANCOAST, M.D., and EUGENE P. PENDERGRASS, M.D.	326
The Effect of Malaria on the Nervous System with Special Reference to the Malarial Psychoses. By CLEMENT B. MASSON, B.S., M.D.	334
The Relation of Fungi Imperfecti to Diarrheal Conditions. By MOYER S. FLEISHER, M.D., and M. WACHOWIAK, M.D.	371
Two Cases of Mycotic Aneurysm, Gonococcal and Pneumococcal in Origin. By B. W. REIFENSTEIN, B.S., M.D.	381
The Human Dying Heart. By MORRIS H. KAHN, M.A., M.D., and ISRAEL GOLDSTEIN, A.B., B.S., M.D.	388
The Surgery of Pulmonary Tuberculosis. By JOHN ALEXANDER, M.A., B.S., M.D.	412
Infection of the Gall-bladder in Relation to Pernicious Anemia. By NOBLE WILEY JONES, M.D., and THOMAS M. JOYCE, M.D.	469
Diabetes Surgery. By M. G. SEELIG, M.D.	495
The Clinical Utilization of Leukocyte Counts with Special Reference to the Use of Graphic Reports. By ROBERT A. KILDUFFE, A.B., A.M., M.D.	502
Composition and Physical Properties of Normal Human Blood. A Compilation of Values from the Literature. By H. C. GRAM, M.D.	511
Low Back Pain as Seen in an Orthopedic Clinic. By J. ALBERT KEY, M.D.	526
The Therapeutic Value of Blood Transfusion: With Report of Sixty-eight Cases of Sepsis. By RUFUS E. STETSON, M.D.	534

The Interesting Behavior of Tuberculous Guinea-pigs under Parathyroid and Calcium Administration: A Preliminary Report. By P. S. PELOUZE, M.D., and RANDLE C. ROSENBERGER, M.D.	546
The Selective Action of the Suprarenal Cortex Secretion on Mesothelial Tissues. By ROBERT C. MOEHLIG, M.D.	553
Epidemic Diaphragmatic Pleurodynia or "Devil's Grip." By ROBERT G. TORREY, M.D.	564
A Protozoan Organism Within the Erythrocytes of Patients Suffering from Epidemic Pleurodynia (Devil's Grip). By JAMES C. SMALL, M.D.	570
The Surgery of Pulmonary Tuberculosis. By JOHN ALEXANDER, M.A., B.S., M.D.	574
Endocrinology from the Point of View of the Surgeon. By G. W. CRILE, M.D.	625
The Diagnosis and Treatment of Exophthalmic Goiter (Graves' Disease). By J. WILLIAM HINTON, M.D.	629
Evidence that Idiopathic Epilepsy is a Sensitization Disease. By JOSEPH L. MILLER, M.D.	635
Some Cardiac Effects of Atropin. By ROBERT DAWSON RUDOLF, M.D., (EDIN.), F.R.C.P. (LOND.), and F.M.R. BULMER, M.B. (TOR.), B.Sc. (Tor.)	641
The Myocardium in Non-Infectious Myocardial Failure. By B. J. CLAWSON, M.D.	648
A Study of Four Thousand Reported Cases of Aneurysm of the Thoracic Aorta. By LINN J. BOYD, M.D.	654
Problems in Hypertension—An Attempt to Correlate Hypothetical and Practical Considerations. By SELMAN NEUHOF, M.D.	668
The Non-calculous Gall-bladder. By RALPH R. MOOLTEN, A.B., M.D.	684
Phenoltetrachlorophthalein in the Study of Liver Function. By W. W. BOARDMAN, M.D., and G. D. SCHOONMAKER, M.D.	688
Observations on the Treatment of Primary and Secondary Syphilis. By B. A. THOMAS, A.M., M.D.	697
The Pathology of Tuberculosis in Infancy, with Clinical Illustrations. By FREDERIC H. BARTLETT, M.D., and MARTHA WOLLSTEIN, M.D.	704
Comparison of Blood-platelet Count in Splenic, Arterial, and Venous Blood. By JACKSON K. HOLLOWAY, M.D., and LAUNCELOT M. BLACKFORD, M.D.	723

Two New Antimony Compounds for Intravenous Use. A Study of Their Therapeutic Value in Cases of Granuloma Inguinale. By ALEXANDER RANDALL, M.D., F.A.C.S.	728
Experimental Biliary Drainage in the Dog. A Preliminary Note. By A. WINKELSTEIN, M.D., and P. W. ASCHNER, M.D.	749
Prognosis in Organic Heart Disease. By GEORGE W. NORRIS, B.A., M.D.	781
The Prognosis of Angina Pectoris. By LOUIS HAMMAN, M.D.	786
Prognosis of the Tachycardias. By JAMES S. McLESTER, M.D.	795
Tumors of the Breast: A Clinical Consideration. By JOHN F. ERDMANN, M.D.	799
The Results of Operations for Chronic Appendicitis (Second Series). By CHARLES L. GIBSON, M.D.	807
The Pressure Factors in the Biliary-duct System of the Dog. By A. WINKELSTEIN, M.D., and P. W. ASCHNER, M.D.	812
Bone Marrow and Spleen in the Treatment of Anemia. By CHAUNCEY D. LEAKE, Ph.D., and JOSEPH S. EVANS, M.D.	819
Splenic Anemia: Report of a Case in a Late Stage Cured by Splenectomy. By EDMUND HORGAN, M.D., F.A.C.S., in collaboration with WILLIAM P. REEVES, M.D., F.A.C.S., and WILLIAM EARL CLARK, M.D., F.A.C.P.	836
Combined Sclerosis of the Spinal Cord and Carcinoma of the Stomach: Report of a Case. By JOHN L. GARVEY, M.D., and LOUIS D. STERN, M.D.	847
The Treatment of Tetanus, with Special Reference to the Use of Magnesium Sulphate. By CARROLL SMITH, M.D., F.A.C.S., and W.E. LEIGHTON, M.D., F.A.C.S.	852
Observation of Fat Digestion for Clinical Study and Physiological Demonstration. By ANTHONY BASSLER, M.D., F.A.C.P., and J. RAYMOND LUTZ, B.S., M.D.	869
Primary Cancer of the Liver. By JULIUS FRIEDENWALD, M.D., and HIRAM FRIED, M.D.	875
The Pathways of the Mediastinum, the Lungs, and the Pleuræ. By J. CURTIS LYTER, M.D.	882
A New Vascular Sign of Death. By MORRIS H. KAHN, M.A., M.D.	890
Auricular Flutter, with Periods of 1:1 Ventricular Response. By THOMAS M. McMILLAN, and JOHN A. SWEENEY	893

REVIEWS

Reviews of Books.	126, 284, 437, 597, 752, 902
---------------------------	------------------------------

PROGRESS OF MEDICAL SCIENCE

Medicine	131, 291, 605, 761, 909
Surgery	133, 294, 445, 607, 911
Therapeutics	136, 297, 448, 609, 762, 914
Pediatrics.	139, 299, 450, 612, 764, 915
Dermatology and Syphilis	142, 616, 767, 919
Obstetrics	145, 302, 454, 769, 922
Gynecology	148, 305, 459, 618, 774, 924
Pathology and Bacteriology	151, 307, 461, 623, 926
Hygiene and Public Health	154, 310, 465, 776, 928

THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

JULY, 1924

ORIGINAL ARTICLES.

THE SURGERY OF PULMONARY TUBERCULOSIS.*

BY JOHN ALEXANDER, M.A., B.S., M.D.,

ANN ARBOR, MICHIGAN.

- | | |
|---|---|
| I. INTRODUCTION. | XI. EXTRAPLEURAL PNEUMOLYSIS. |
| II. THE EVOLUTION OF SURGICAL THERAPY. | XII. OPEN INTRAPLEURAL PNEUMOLYSIS. |
| III. PATHOLOGICAL ANATOMY AND PHYSIOLOGY. | XIII. CLOSED INTRAPLEURAL PNEUMOLYSIS. |
| IV. THORACOPLASTY COMPARED WITH ARTIFICIAL PNEUMOTHORAX. | XIV. PARALYSIS OF THE DIAPHRAGM |
| V. INDICATIONS AND CONTRAINDICATIONS. | XV. TUBERCULOSIS CAVITY OF THE LUNG. |
| VI. CHOICE OF OPERATION. | XVI. TUBERCULOSIS EMPYEMA. |
| VII. PREOPERATIVE MANAGEMENT. | XVII. POSTOPERATIVE COURSE, COMPLICATIONS AND MANAGEMENT. |
| VIII. ANESTHESIA. | XVIII. DEFORMITY. |
| IX. SAUERBRUCH'S EXTRAPLEURAL PARAVERTEBRAL THORACOPLASTY. | XIX. RESULTS. |
| X. BRAUER'S SUBSCAPULAR EXTRAPLEURAL PARAVERTEBRAL THORACOPLASTY. | XX. CONCLUSIONS. |
| | XXI. BIBLIOGRAPHY. |

Synopsis. The length of this paper requires that it appear in several installments. I therefore present here the following observations, which will be developed in the text:

1. On account of pleural adhesions, many patients with pulmonary tuberculosis that is mainly unilateral do not obtain from artificial pneumothorax the full benefit of lung compression therapy.

2. Many among them are in sufficiently good general physical condition for surgery. The operation of choice is paravertebral thoracoplasty.

* From the Department of Surgery, University of Michigan.

3. Any tuberculous lesions in the better lung should be inactive or only slowly progressive, if surgery is to be undertaken.

4. Cauterization, under thoracoscopic vision, of adhesions that are preventing adequate lung compression by pneumothorax should be reserved for those that are long, narrow and few in number.

5. In suitable cases operation should be performed as soon as artificial pneumothorax has proven itself ineffective; procrastination may rob these patients of an excellent chance of complete cure.

6. Thoracoplasty should be done in two stages, from two to three weeks apart. No fewer than 125 cm. of ribs XI to I inclusive should be resected.

7. Local and regional anesthesia is indicated for patients whose daily expectoration is more than 40 cc. When less than 40 cc, a combination of nitrous-oxide-oxygen narcosis and local and regional anesthesia is best.

8. The immediate and remote dangers of any operation that compresses only a part of a hemithorax are greater than its advantages, except in unusual cases. This does not apply to a combination of partial thoracoplasty and partial artificial pneumothorax.

9. Neurexairesis of the phrenic nerve may be performed with advantage before every thoracoplasty and after every artificial pneumothorax.

10. Some stiff-walled apical cavities are not obliterated by paravertebral thoracoplasty. The supplementary operation of parasternal thoracoplasty, or of pneumolysis with muscle, fat, gauze or paraffine "fill" should be considered, but not performed sooner than six months after the primary operation.

11. Some cavities cannot be collapsed, and by retention of secretions cause severe toxemia. Drainage is occasionally indicated for them.

12. Tuberculous empyema is best treated by repeated aspirations and air replacements, and sometimes with antiseptic instillations or irrigations. Only in the presence of dangerous secondary infection may open or close tube drainage be used. Persistent empyemas, especially if complicated by fistula, often require thoracoplasty for their cure.

13. Favorable results in the surgery of pulmonary tuberculosis depend upon great discretion in the selection of cases, early and skilfully executed complete operations and strict attention to post-operative care, including not less than six months "curing," preferably at a sanatorium.

14. Among 1024 cases of advanced tuberculosis, reported from 1918 to 1923, there was a mortality of 12 per cent during the first month after operation (the immediate operative mortality was about 2 per cent), and 19 per cent thereafter, mostly from tuberculosis in the originally better lung or other organs. Twenty-six per cent were improved, and 32 per cent were cured. Of the 824 patients

managed according to the criteria given in paragraph 13, immediately above, 26 per cent were improved, and 33 per cent cured.

I. Introduction. A therapy for certain selected cases of desperate advanced pulmonary tuberculosis that cures 33 per cent of the patients, and improves an additional 26 per cent, deserves and demands more rapid adoption in the United States than it is now receiving. It may be conservatively estimated that at present there are in this country 15,000 persons with pulmonary tuberculosis for whom surgical interference is indicated, many of whom are living at home, too diseased for admission to sanatoria, spreading infection and unable to work, and, if unaided, almost certainly doomed to die.

Except when especially indicated to the contrary, the various divisions of this paper concern themselves with the operation of paravertebral extrapleural thoracoplasty (resection of the posterior ends of the ribs), upon which, as a foundation, modern surgery of pulmonary tuberculosis is built.

Within the past five years Sauerbruch of Zurich and Munich has alone reported over 500 operated cases, while the total number from all clinics in the United States and Canada is 110. Archibald of Montreal was the first to operate in America (1912), and has since performed 40 additional operations. Shivers of Colorado Springs has operated upon 27 patients since 1914, Lilienthal of New York 12, Law of Minneapolis 11, Welles of Saranac Lake 11, Eloesser of San Francisco 5, Willy Meyer of New York 5; and there have been other smaller series. During fifteen years and more, surgical compression therapy has been developed and extensively practised in Switzerland, Germany, Scandinavia and Denmark, and has earned for itself a sure and permanent place. North and South America, England, Spain, Italy, Belgium and France are only now commencing to be aware of its remarkable value, and to use it.

The reasons why these last named countries have delayed so long are easily understood. Chief among them is ignorance of the method, its indications, execution and results. This lack of familiarity is not suprising in view of the fact that it has always been a slow process for highly specialized procedures to overcome international language barriers. In view of the known facts, however, it is discouraging to find only three pages devoted to the method in the 1922 edition of a standard American text-book on tuberculosis, and only nine small pages in a 1920 volume of a 32 volume French system of medicine, and both of these accounts uninformed, inaccurate and misleading. Other recent books cite the technic and results of the Brauer-Friedrich and the Lenhartz operations of fifteen years ago as illustrative of modern technic and results, and completely ignore the revolutionary changes brought about by the two-stage.

paravertebral operation. On the other hand, it is somewhat encouraging to know that such an authority as Krause has recently written that the German results warrant more extensive use of surgery, and that he believes that the method will be accepted by the profession for certain advanced forms of the disease.

There exists today among many physicians and patients a hazy notion that the operative shock and mortality are terrific, the post-operative pain scarcely endurable, and that the survivors, grossly mutilated and crippled, may only hope to drag themselves through a few extra years of burdensome life, and, indeed, that permanent clinical success is a rarity. That this notion is not based upon fact is evident to anyone who is acquainted with present day technic and results.

A further not insignificant reason for the unduly slow popularization of surgical compression therapy is that certain monographs, purporting to represent and illustrate standard procedure, but actually describing inefficient, if not dangerous methods, appear from time to time, and are obliged to report such high mortalities and poor final results that those seeking information are driven away from surgery rather than informed and attracted. Indications and contraindications are often badly placed, and bizarre operative technic described. Probably the two greatest sins are: (1) the reporting of cases as operated upon by the "Sauerbruch technic" when the first rib has not been touched (except in rare cases resection of a portion of that rib is an essential step in the operation), and (2) the use of partial operations, half-measures, when the widest experience has demonstrated that only total operation may be expected to produce the successful result desired.

As no comprehensive survey of modern compression therapy exists in the English language, it is the purpose of this paper to outline a standard procedure that may be expected to give the best results in the light of modern knowledge, in the hope that it may help the profession to understand and to popularize it some years in advance of the time when it would "arrive" by the normal processes of diffusion. The paper is based upon a critical review and analysis of the world's literature of the past six years.

Artificial pneumothorax is now firmly established in this country, and where indicated is being used often and early, frequently with miraculous results. When, on account of pleural adhesions, satisfactory compression cannot be obtained with air, equal and sometimes better results are obtainable with surgery. Although there is now an increasing reluctance among physicians to condemn surgical compression in pulmonary tuberculosis "on general principles," as many did a few years ago, it is as yet rarely advised, largely I think, because it is so little understood outside of Central Europe. Skilful surgical management demands special knowledge and training, and until a greater number of well-grounded surgeons

have manifested their interest and properly equipped themselves, tuberculosis specialists and physicians in general will be very reluctant to recommend to their patients so specialized an operation. Once the surgeons have demonstrated their interest the internists will speedily avail themselves of the opportunity.

II. The Evolution of Surgical Therapy. The surgical therapy of pulmonary tuberculosis has followed many blind paths; it has been only during the past thirty-five years that the present type of operation has been in process of development.

Drainage of tuberculous cavities has been practised in isolated cases for many centuries, but rarely advocated with enthusiasm. In 1885, de Cereville, however, published a small series of personal cases and believed that the method had a promising future. In recent years Sauerbruch has become a strong advocate of drainage in selected cases.

Many unsuccessful attempts have been made to influence the progress of tuberculous lesions by direct application of medicaments by the tracheal or intercostal routes. Baglivi in 1696 introduced them after intercostal incision. Mosler in 1875 injected phenol and other drugs through a needle directly into the areas of maximum pathology, as well as into cavities after aspiration of their contents. Koch used tincture of iodine. Gessner in 1904 reported not unfavorable results (cough and sputum somewhat reduced) from the injection of iodoform and glycerin, or zinc chloride, or alcohol. The drugs were intended to disinfect and to stimulate the growth of fibrous tissue. As they could reach only a very small number of the diffuse lesions these actions must be without notable, favorable results. The dangers of causing sloughs, and of injecting highly irritating drugs into bloodvessels or bronchi are considerable.

In 1858, Freund started a controversy that only now is dying. He claimed after extensive postmortem observations that active apical tuberculosis was more common in those whose first rib was shorter, or whose first cartilage was stiffer than normal, and that not infrequently he had seen healing in such cases where there had been spontaneous rupture of the cartilage and new joint formation. He believed that the stenosis of the upper thoracic aperture caused an insufficient blood supply, and stasis of lymph and bronchial secretions, and consequently lodgment and growth of any tubercle bacilli that might happen to be present. That apical tuberculosis only rarely occurs in children he explained on the ground that in them the apex is normally below the first rib, and therefore uninfluenced by its abnormalities. Concretely, he proposed to section, or partially to resect the first cartilage, thereby mobilizing the apex, and permitting it to share in full respiratory excursions. Freund's contentions were strongly supported by Hart and Harris and by many others. Bachmeister showed experimentally that artificial narrowing of the thoracic inlet determined the localization of tuber-

culosis. Many pathologists have noted the concentration of tubercles beneath the groove (Schmorl's) sometimes made in the lung by the first rib. Recently Kaiser, of Jessen's Clinic, has reported a study of 600 roentgenograms, from which he concludes that the localization and development of tubercles is definitely determined by the ossification, narrowness or anomalous position of the thoracic inlet. Walker in 1919 reported the combination of apical disease and stenosis in 54.29 per cent of 35 dissected cases, and presented a mathematical formula for determining the size of the inlet.

Kausch has performed the Freund operation 9 times, and 7 were improved or cured. At present those who accept the Freund theory are unanimous in condemning the operation as being too radical for very early lesions, and ineffective for developed ones, but do advocate the systematic use of breathing exercises as prophylaxis against tuberculosis where inlet stenosis exists. Sauerbruch suggests possibly using Freund's operation upon a healthy child, with inlet stenosis, who has been exposed to tuberculous infection, and whose chest is so inelastic as to be uninfluenced by breathing exercises.

At present a majority of clinicians deny the validity of the theory, claiming that the figures offered in support of it are far from convincing, and that the ossification of the first cartilage is frequently a sequel of the tuberculosis, rather than a primary determining factor. Hofbauer points out the danger of checking the further growth of the first rib of a child by operative interference with its epiphysis. Kausch, Blanc and Fortacin, and others have said with much reason that the removal of a small section of the first cartilage causes rest and a small compression of the apex, and not an increase in respiratory excursion, and that any favorable results that may have been observed were due to a true thoracoplasty, although a very small one.

It is not surprising that actual resection of diseased lung tissue should have been attempted, after successful experiments upon animals. Tuffier, Lawson, Doyen, W. Macewen and Sauerbruch have reported successful operations upon man; Block, Ruggi, von Herff, W. Müller and Réclus have also done it, but unsuccessfully, and usually with fatal results. In all there have been only 3 or 4 somewhat permanent cures, and 7 reported deaths. The objections to such an operation are outstanding: (1) Pulmonary tuberculosis is almost never strictly localized to one lobe, or to a part of a lobe, and there is almost always lymphatic extension to the hilus. Therefore conservative resections cannot extirpate all of the disease; (2) unless the resection were small enough to permit the vacant space to become filled by the shifting of neighboring organs, or by compensatory emphysema, a subsequent thoracoplasty would be necessary to obliterate it, thereby exposing the patient to the dangers of two major operations; (3) sanitarium treatment offers most excellent chances of cure for those localized, minimal lesions for which resec-

tion might be considered indicated, and is without risk. The only modern indication for resection is where one entire lung is almost completely destroyed by cavity formation, and the other lung is in fair condition; under differential pressure anesthesia, a wedge including the huge cavity should be removed. The successful cases of Macewen and of Sauerbruch, noted above, were of this type.

The favorable influence of pleural effusions and of spontaneous pneumothorax (if the patient survives the shock) upon largely unilateral pulmonary tuberculosis has been known for many years. Spaeth remarked it in 1850, and more recently von Muralt has reported the cure of 6 out of 33 patients in whom spontaneous pneumothorax had occurred. Such observations suggested to Forlanini in 1882 the use of artificial pneumothorax, and were also responsible for the independent development of pulmonary compression by rib resection. It is a curious fact that for more than twenty years it occurred to no one that the effect of artificial pneumothorax and of thoracoplasty upon tuberculous lungs was exactly the same—a mechanical relaxation or compression, and it was not until then (1907) that Brauer laid down the hard and fast rule, which holds inflexibly today, that primary thoracoplasty is never indicated when a satisfactory compression is obtainable with artificial pneumothorax.

One hundred years ago James Carson predicted that if a cure were to be found for pulmonary tuberculosis it would be by surgical operation, effecting a mechanical compression that would put the diseased parts in a quiescent state. In 1885 the first attempts in this direction were made by de Cernville of Lausanne, thereby initiating the method that is used today. The operative technic of all his work and of the many subsequent modifications was based upon the operations which had already been performed by Simon (1869), de Cernville (1877) and Estlander (1879) for chronic empyema. de Cernville's 1885 report demonstrates that he understood the necessity of breaking the continuity of the bony, non-yielding thoracic cage, in order to effect collapse of pulmonary cavities. He operated in 4 cases of apical cavity, 2 of which he drained; although he resected only 3.5 cm. of the second and third ribs anteriorly, or "as many as necessary, according to the extent of the cavity," he observed definite pulling in of the sectioned ribs and consequent lessening of the size of the cavities. Independently, Quincke did the same thing in 1888, and in 1896 urged small rib resections for non-cavernous types of tuberculosis as well. Independently of him Carl Spengler in 1890 resected greater lengths of ribs from under the scapula via a periscapular incision in cases in which pleural effusions had occurred; he aspirated the effusions before operation. Spengler called his operation "extrapleural thoracoplasty," the name used today for the standard operation. Turban in 1899 also operated for non-cavernous types of tuberculosis, and

resected as many as 65 cm. of ribs IV to X. In 1901 and 1903 Garrè and Quincke first urged thoracoplasty for hemoptysis, and advocated supplementing it with an extrapleural pneumolysis. In 1902 Landerer resected from 4 to 8 cm. of ribs I to V anteriorly, or ribs II to VIII, or IV to IX posteriorly.

The results of all of the preceding procedures were unsatisfactory, and Brauer realized that clinical success depended upon obtaining a pulmonary compression comparable in amount with that obtained by artificial pneumothorax, which was already effecting remarkable cures. Therefore, instead of the limited resections practised hitherto he proposed the removal of the entire lengths of ribs II to X at one sitting, in order to obtain actual compression of lung, instead of mere relaxation. Friedrich, his surgeon, first operated by this method in December, 1907, and the result was highly satisfactory. However, in their series of 29 cases there were 8 operative deaths, a mortality of 27.5 per cent; there were 6 complete cures, 20.7 per cent. Lenhartz used the same technic, and in addition pressed the apex toward the hilus, and killed 19 of 20 patients. Sauerbruch has used the Brauer-Friedrich technic upon 71 patients, 62 of whom, however, he operated in two or more stages; his only operative deaths, 2 in number, occurred after single stage operations. His combined early and late deaths totaled 31 (43.6 per cent), his improvements 12 (16.9 per cent), and complete cures 28 (39.4 per cent).

It was soon realized that this operation was highly dangerous. The operative shock was terrific; the side of the chest operated upon, being deprived of all of its bony support, swung in and out freely with the respiratory movements, but in a paradoxical sense, and this swinging was shared by the mediastinum (unless it was firmly fixed by adhesions), and consequently the opposite lung was narrowed, respirations became rapid and superficial, the circulation not infrequently failed, and many patients soon died of acute respiratory insufficiency. Because of the labored respirations of the opposite lung, rapid progress of minimal lesions there was frequently observed.

At first Friedrich operated rapidly under light general narcosis, supplemented by local anesthesia. Through a Schede incision (horseshoe-shaped: down the front of the chest, across it laterally and up between the spine and scapula) he removed 10 to 25 cm. each of ribs II to X (together with their periosteum and intercostal muscles), a total of 130, 160 or 200 cm., leaving the first rib in order to save time, expecting it to become depressed as the chest gradually narrowed. Later he modified this technic by using regional and local anesthesia alone, operated more slowly, resected the first rib as he found he could not count upon its "settling" enough to give satisfactory apical compression, left the anterior ends of the ribs as he saw that they helped greatly to prevent chest flutter, and that

they bent in at the cartilages as pulmonary scar tissue contracted, and left the periosteum and intercostal muscles intact, as lung herniæ were common when they were removed. As thus modified, it will be seen that the Brauer-Friedrich operation was similar to an Estlander operation for chronic empyema.

At present the Brauer-Friedrich operation is obsolescent because of its many dangers. It is still sporadically used for rare cases where the pleura and mediastinum are known to be so thickened by adhesions that mediastinal displacement and flutter are not to be feared. Even then it would be used only by dividing it into two or more stages.

Brauer has modified this original operation of his, eliminating the major dangers and yet obtaining great compression and excellent clinical results. It will be described in a later instalment.

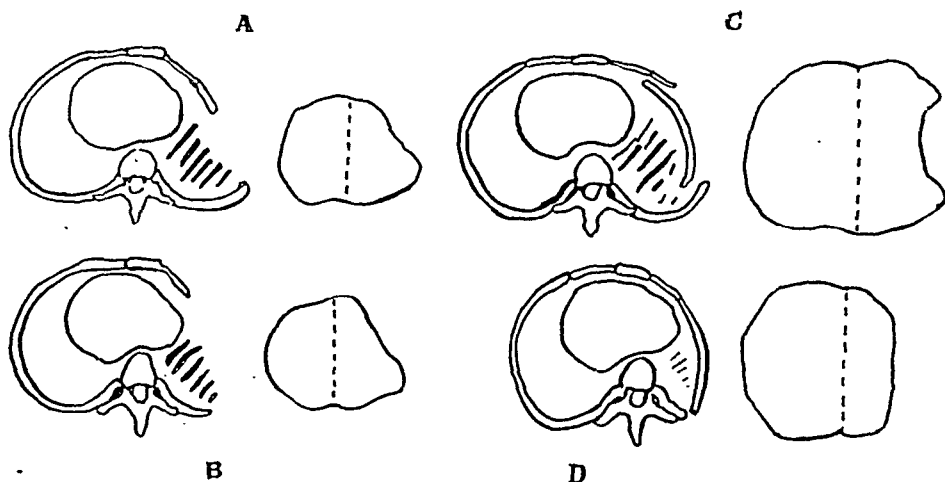


FIG. 1.—Diagrams illustrating the relative reduction in capacity of the hemithorax after various types of rib resection. A, Estlander technic: five ribs resected; chest circumference reduced 4 cm.; B, Gayet-Estlander: 110 cm. resected from eight ribs; circumference reduced 5.5 cm.; C, Quénu: small resections of seven ribs; circumference reduced 3 cm.; D, Boiffin-Gourdet: 54 cm. resected from nine ribs; circumference reduced 8 cm. It is this type of resection that is used in the modern operation for tuberculosis. (After Brauer and Spengler, from Boiffin and Gourdet).

In 1923 Davies proposed a modification of the Brauer-Friedrich operation that seems to have almost nothing to recommend it. He makes a long vertical incision in the midaxillary line and resects ribs II to IX from their costochondral junctions to about their angles. He states that the first rib needs removal only rarely, as the whole anterior and lateral chest sinks in; if it requires removal later, it could be done through a separate incision below the clavicle, he says. The disadvantages of this operation are that it exposes the patient to the dangers of the Brauer-Friedrich operation, and does not take advantage of the fact, well-known since the beautiful demonstrations of Boiffin and Gourdet, that removal of those parts

of the ribs posterior to their angles (over the costovertebral gutter) is essential for satisfactory compression; further, it is firmly established that in a huge majority of cases it is necessary to resect the first rib in order to compress the apex, which is apt to contain the most advanced disease. Bayer, C. Spengler and Sauerbruch have also removed lateral rib sections through an axillary incision, but abandoned this technic as the anterior and posterior rib stumps were seen to spring out instead of to fall in. This same springing-out has been noted when only the anterior ends of the ribs are removed, parasternally.

As the Brauer-Friedrich operation was a reaction against the restricted resections of the earlier thoracoplasties, so the present types of operation are compromises between the two—extensive enough for favorable clinical effect, and yet conservative enough to avoid unusual operative dangers.

Wilms realized that the removal of short lengths of ribs at their posterior ends, that is, from just in front of their angles all the way to the transverse processes of the vertebræ, would not only give relatively great reduction in the chest capacity, without chest-wall and mediastinal flutter, but that it could be done without operative shock. There was not an operative death in his series of 23 cases. At first he resected only from 2 to 4 cm. of ribs I to V paravertebrally, and at a second sitting two to four weeks later, 2 to 4 cm. of rib-cartilages I to V parasternally. This operation is known as "Wilms columnar resection." He soon saw that better results would be obtainable by extending his resections further beyond the limits of gross disease; he then resected as far down as the seventh or eighth rib posteriorly and the sixth or seventh anteriorly, operating in two or three stages. At this period he did not fear aspiration into the lower lobe of infected secretions which were pressed out of the upper lobes by thoracoplasty. By 1913 he was well aware of this danger, and removed, at the *first* sitting, from 10 to 20 cm. of ribs VII, VIII and IX, and lesser lengths of the mid-ribs; at a second sitting, 4 to 5 cm. of the upper ribs, including the first; at a third sitting, 2 to 3 cm. of ribs I to V parasternally, and possibly the inner end of the clavicle, in order to obtain the compressing weight of the shoulder against the lung. At the present time he never resects the clavicle, and only exceptionally adds the parasternal resections.

Sauerbruch, once Friedrich's assistant, should be given great credit for having urged and practised many of the improvements which are part of the final Wilms technic, and in fact this operation is now generally known by the name of "Sauerbruch's paravertebral extrapleural thoracoplasty." It was Sauerbruch who insisted upon doing the posterior operation in more than one stage, and in removing the lower ribs first to check the lower lobe's respiratory function in order to lessen the chances of aspiration when the more extensively diseased upper lobes were later compressed. It was he who urged

local and regional anesthesia, and proposed the convenient hook-shaped incision, embracing the angle of the scapula. With his tremendous experience of over 500 cases, his opinion in regard to the surgical therapy of pulmonary tuberculosis is generally accepted as law.

In recent years a number of rather bizarre operations have been proposed, but none of them have gained favor, or are likely to. In 1913 Alvarez operated upon 4 cases of advanced tuberculosis, stretching the second, third and fourth intercostal nerves in order to paralyze, by excess of stimulation via the rami communicantes, the vasoconstrictor fibers of the sympathetic nerves to the lung. He hoped to produce an active congestion of the lung and, so, favorably to influence the disease. He reported that mild to absolute dulness occurred for from three to six days after these operations, and that there was noted a temporary clinical improvement—better appetite, weight and sleep, less sputum and fever. The improvement was only temporary, and 3 of the 4 soon died. Codina has reported a case which was markedly improved, as shown by a loss of tubercle bacilli and a gain of 7 kg. in weight in two months. Friedrich and Warstat practised the operation and their results were poor. Alvarez now proposes resection of the second, third and fourth sympathetics within the chest (extrapleural approach), hoping to obtain a permanent congestion of the lung. This modification has never been used upon man, but Lapeyre has done it upon normal dogs. As at present developed, there is nothing better than poorly supported theory in favor of Alvarez's sympathetic operation.

Bruns and Sauerbruch have proposed ligation of lobe branches of the pulmonary artery, and Tiegel of the vein, in order to cause dense fibrosis of the lobe. Artery ligation has been used with some success for bronchiectasis in man, but the adhesions in most cases of advanced pulmonary tuberculosis would prevent ready access to the hilus. However, in 1923 Schlappfer advocated a combination of ligation of the pulmonary artery and phrenicotomy for tuberculosis in man; he would expect this to effect clinical healing, or prepare the lung for a relatively safe secondary lobectomy, which would eradicate remaining foci. He further proposed partially to occlude the pulmonary veins with Halstead bands, which would later be removed, as a "partially curative, partially preventative" measure against slight unilateral tuberculous infection in the presence of a strong tuberculous family history. Two important objections may be made to these propositions: (1) the rather extreme pulmonary fibrosis that would follow either operation would probably demand subsequent thoracoplasty to compensate for the traction displacements produced, in spite of the phrenicotomy; (2) any intrapleural operation, involving the separation of adhesions, upon an actively tuberculous person has proven gravely dangerous.

Artificial pneumothorax and thoracoplasty now offer such excellent chances of success that they will not give place to such dangerous and complicated procedures as these.

Experimentally Henschen has produced great pulmonary fibrosis by: (1) sewing the fascia lata tightly over one or more lobes, or (2) displacing the lower lobe beneath the diaphragm, through an incision in its fibers, or (3) severing the attachments of the diaphragm, thereby allowing it to rise (even as high as the second rib), and compress the lung.

Warstat has experimentally resected or stretched all the intercostal nerves on one side, and he observed a great flattening of that side—a “cadaveric position” with almost no respiratory movements, and marked fibrosis of the lung. Into some of his operated animals he injected tubercle bacilli intravenously, and at necropsy saw the usual active, large, caseous tubercles in the lung of the unoperated side of the chest, but only small, non-caseous tubercles on the compressed side. He then operated upon two men with cavity formation, one of whom had had a previous phrenicotomy; in both there was great flattening of the operated side, and no harm from the abdominal wall paralysis. Morales twisted out 12 intercostal nerves on one side in several cases, and obtained favorable results in a few. As the intercostal nerve operations are nearly as severe as Sauerbruch’s thoracoplasty, and are less effective, and as there is some danger of tearing the pleura while searching for the nerves, it is not likely that these operations will ever become popular.

In 1917 Kronberger proposed and practised resection of sections of alternate ribs, or 2 out of every 3 ribs, on the theory that it would permit considerable lung retraction and at the same time preserve the function of that lung, and not threaten the circulation. As this major operation produces no compression or rest of the diseased parts, but only a small relaxation, it will never gain favor.

III. Pathological Anatomy and Physiology.* Sauerbruch cites the history of a patient upon whom he performed thoracoplasty on account of repeated hemorrhages and cavitation in one lung, in spite of active disease in the other lung; the patient died three months later. There was seen at necropsy a definite tendency to encapsulation, with young connective tissue, of all tubercles and caseous nodules in the compressed lung; its cavities were mere clefts, which were being filled with new granulation tissue containing many bloodvessels. The uncompressed lung showed new cavity formation and extensive caseous pneumonia, but *without any tendency whatsoever toward encapsulation*. That the far-advanced lesions in the compressed lung of a dying person were able to progress so far toward arrest in a period of three months is illustrative of the effect of compression. Jessen is correct in saying that the problem of advanced pulmonary tuberculosis is a mechanical one, as well as an immunological one.

* Also see DEFORMITY.

While bed-rest considerably quiets respiration, it is not able to put the lung at complete rest, nor to protect it against the violent movements of coughing. Compression therapy not only does this, and thereby largely checks the movement of toxin-laden lymph into the general circulation and of bacilli-laden lymph to new situations in the lungs, but empties the lungs of accumulated products of degeneration, and, by flattening the lumina of the bronchi and alveoli, prevents the spread of infection by the bronchial tree route; most important of all, it is directly responsible for a rapid new growth of fibrous tissue which encapsulates the lesions and eliminates the disease.

There is some difference of opinion as to how much thoracoplasty lessens the capacity of the chest; this depends considerably upon the lengths of ribs removed, and upon whether or not the sections

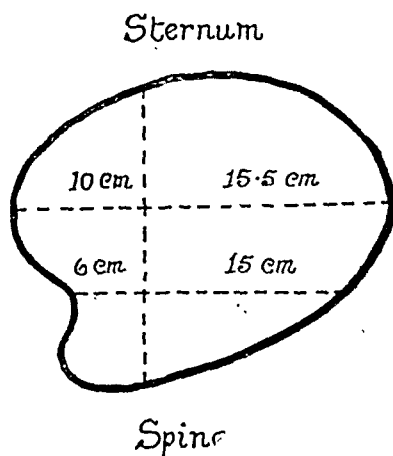


FIG. 2.—Cyrtonetric diagram showing diminution in area of the left hemithorax following paravertebral thoracoplasty. (After Bérard and Dumarest.)

between the angles and heads of the ribs have been resected. Over thirty years ago Boiffin and Gourdet showed upon cadavers that if these portions were included in the resections, removal of a total of 54 cm. from 9 ribs reduced the chest circumference 8 cm., whereas if these portions were not removed and the resections were made anterior to the rib angles, a total of 110 cm. from 8 ribs would reduce the chest circumference only 5.5 cm. (see Fig. 1). Saugmann, who removed an average of 134 cm. from 10 ribs and included their posterior extremities, found at a necropsy a reduction of from $\frac{1}{3}$ to $\frac{1}{2}$ of the normal chest capacity. Sauerbruch says that after his operation the chest capacity is reduced only 300 to 500 cc; Brauer says that his radical thoracoplasty effects a reduction of 3000 cc, which corresponds to two-thirds the volume of a complete pneumothorax. Madinier considers the amounts of compression of the lung after a good thoracoplasty and a large partial pneumothorax approximately equal. The clinical results given under thoracoplasty compared with artificial pneumothorax show that thoracoplasty is

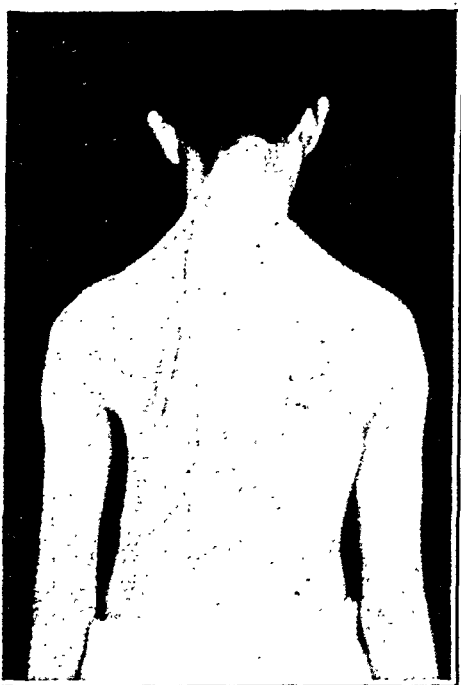
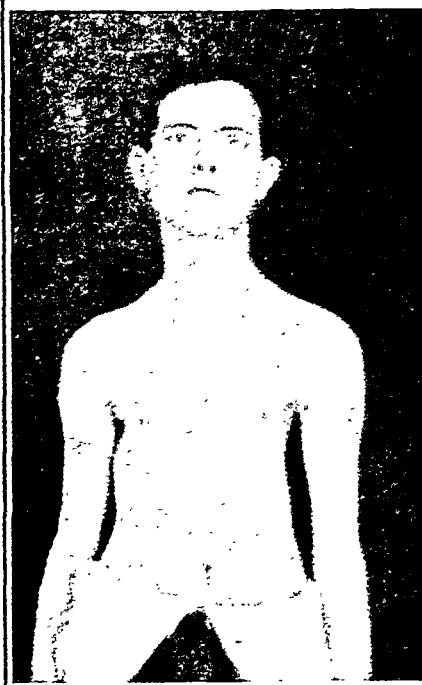


FIG. 3.*—A. H., one year after paravertebral thoracoplasty. Inconspicuous scar. The small amount of apparent gross deformity should be compared with the actual reduction in chest capacity as shown in Fig. 5.

Before operation this patient was in poor condition, confined to bed, weighed 114 pounds (normal, 126 pounds); temperature 99.6° , pulse 90; left lung, far advanced tuberculosis with cavity in upper lobe; right lung moderately advanced tuberculosis; 150 cc sputum daily; blood-streaked and positive for tubercle bacilli; had "cured" for two years. At the time these photographs were taken, one year after operation, he was in good condition, weighed 130 pounds; temperature normal, pulse 76; cavity obliterated, right lung inactive; 10 cc sputum daily and steadily decreasing, and tubercle bacilli absent; still under treatment at sanitarium. Further illustrations of this patient will be seen in Figs. 4, 5, 12, and 13.

* Figs. 3, 4, 5, 12, 13 and 14 have been courteously furnished by Dr. E. S. Welles, of Saranac Lake, N. Y.



FIG. 4.—A. H., before operation. Far advanced tuberculosis of whole left lung; cavity upper lobe. Moderately advanced disease of right lung.



FIG. 5.—A. H., one year after operation. Cavity obliterated. Compare with Figs. 3, 4, 12 and 13.

not inferior to pneumothorax because of its producing less complete pulmonary compression.

As thoracoplasty removes the posterior ends of the ribs and as the gaps are usually filled with new bone without joint formation, the bony cage on the operated side is no longer able to share in respiratory movements, and as dense pleural adhesions soon follow the operation, the diaphragm becomes fixed and greatly restricted in function. On the other hand, the removal of great lengths of rib, as in the old Brauer-Friedrich operation, leaves a flaccid chest wall which may not become fixed by new bone formation and which swings inward with inspiration, and outward with expiration—a paradoxical movement which allows the stale air within the collapsed lung to be drawn into the uncompressed lung during inspiration, and blown back into the collapsed lung during expiration—so-called “pendulum respiration.” Further, the effect of any movement, paradoxical or otherwise, upon the grossly diseased lung is in opposition to one of the chief aims of the treatment, namely rest. As the Sauerbruch operation removes only short lengths of rib, the heavy overlying muscles, and, later, new bone formation prevent unfavorable movements of the compressed lung. Although Hug found some paradoxical respiration, usually posterolaterally, in 21 out of 22 of Sauerbruch’s and Schreiber’s patients at Davos, it was never of marked degree.

Cloetta has clearly shown that a moderate pulmonary compression, such as occurs with the modern thoracoplasty or with a moderate pneumothorax, causes a greater, rather than a lesser blood supply to the lung, because when the lung is fully expanded in its normal position the bloodvessels are stretched and narrowed, but when the lung is relaxed the vessels are relaxed and broadened. Microscopically the vessels are seen to be dilated. However, if the pulmonary compression is great the bloodvessels are narrowed and the blood supply is definitely less, and this is contributed to by whatever shrunken fibrous tissue exists in the lung. So, whether a compressed lung is better or worse supplied with blood depends upon the degree of compression and upon the amount of scar tissue it contains. The right heart does not hypertrophy to any appreciable extent unless the pulmonary blood-pressure is definitely raised.

Experiments with lamp black have shown that the flow or stasis of lymph in the lungs is largely determined by the respiratory movements. It follows, therefore, that thoracoplasty determines a lymph stasis, and this is seen to be the case by examining microscopic sections of such lungs: the lymph vessels are markedly dilated and there is great deposition of pigment around them. As stated above, this stasis prevents dissemination of bacillary emboli to unaffected parts of the lungs, and checks the constant “tuberculinization” of the system with the toxic products of the tubercle bacilli; it is this action which is chiefly responsible for the rapid

clinical improvement of patients after pulmonary compression. Stasis of toxic lymph is believed to be responsible for the stimulation of the connective tissue to grow and encapsulate the tuberculous lesions.

Saugmann has spoken of the compressed lung being emptied of its waste products "like a pressed sponge." The elimination of excess tubercle bacillus-carrying secretions from the bronchial tree, and from cavities eliminates one of the most dangerous sources of spread of infection in advanced tuberculosis. Once the loose exudate and semisolid masses are squeezed out much inflammation quickly subsides. Even maximum compression flattens only the alveoli and small-medium sized bronchi; those bronchi protected by heavy cartilage remain open, and, as the pulmonary parenchyma contracts with fibrous tissue, they tend to bronchiectatic widening. Sometimes, however, new fibrous tissue will work in between the mucous membrane and cartilage of the larger bronchi and fill their lumina.

Examination of a compressed lung, which has successfully controlled its tuberculous lesions, shows a fleshy mass, full of connective tissue which is particularly evident around the blood and lymph vessels and bronchi, and as septa radiating from the subpleura. Some of the bloodvessels may be thrombosed. The tubercles are dry, and are seen to be firmly encapsulated by fibrous tissue which either just surrounds them or grows through and through them. If any new tubercles are found, which is rare, they are small, non-caseous and contain many giant cells. Von Muralt says that the healing effect of pneumothorax compression is sometimes so permanent that if an arrested case later becomes actively tuberculous, the disease may be entirely in the formerly better (uncompressed) lung!

These favorable effects of compression are apt to be seen only upon disease that is predominantly proliferative or fibrous in character, as the connective tissue for the encapsulations seems to arise largely from that which has already formed in an unsuccessful attempt to cure. As there is little tendency toward connective tissue formation in exudative lesions, lung compression is less likely to be followed by fibrous encapsulation.

Ample necropsy material has shown that the amount of connective tissue in a compressed tuberculous lung is far in excess of that in an uncompressed, tuberculous lung, and that it will form in cachectic persons in whom it could not be expected, were the lung uncompressed. Henschen asserts that the amount of new connective tissue roughly corresponds with the degree of compression, and, of course, with its duration. Factors responsible for the growth of fibrous tissue in compressed lungs are: (1) stimulation by toxins in the stagnant lymph; (2) chronic hyperemia; (3) cessation of lung function.

(To be continued)

THE USE OF RADIUM RADIATIONS IN THE TREATMENT OF TONSILS: A FURTHER REPORT.*

BY FRANCIS H. WILLIAMS, M.D.,¹

BOSTON, MASS.

THE problem of caring for the tonsils deserves careful study, because of disease in these organs themselves and of the complications in other parts of the body, originating in the tonsils, that diminish the well-being and economic value of a large number of persons.

The fact that lymphoid tissue, particularly when diseased, is easily acted upon by radium makes this remedy of especial value for treating the tonsils or other lymphoid tissue in the throat. Judging by the tests kindly made for me by Dr. F. H. Slack, a director of the Sias Laboratories, Brookline, Mass., the results obtained by the use of radium when short exposures are made are not due to a bactericidal action of this remedy. In these tests the cultures were exposed twenty minutes to 38 mg. of radium element placed at a distance from them of 0.25 cm., the filter used being of aluminum 0.29 mm. thick. Dr. Slack reported as follows: "I exposed freshly planted cultures of *Staphylococcus pyogenes aureus* and of *Streptococcus viridans* to the action of your radium for twenty minutes each. It had no inhibitive action at all upon the growth of these bacteria, the exposed cultures and the controls growing equally well."

My method of treating the tonsils with radium is carried out with instruments that I have devised for the purpose, by means of which the desired amount and quality of the radiations² may be applied under good illumination to the parts to be treated while the other parts are shielded.

Container, Diaphragms and Filters. The container (Fig. 1) is made of gold, because the amount of radiations penetrating a suitable thickness of this heavy metal is small, and has an aluminum cover, 0.29 mm. thick, that allows many times as much radiation to pass through it as does the gold portion of the instrument. The container is so made that when its position is changed the radium

* Read by title at a meeting of the Association of American Physicians, May, 1923.

¹ Treatment of Hypertrophied Tonsils and Adenoids by Radium: A Preliminary Statement, *Boston Med. and Surg. Jour.*, 1921, 184, 256. The Treatment of Tonsils by Radiations from Radium Salts Instead of Operation; 101 Cases, *Trans. Assn. Am. Phys.*, 1922, 37, 204; *Boston Med. and Surg. Jour.*, 1922, 187, 412. *Traitement de l'hypertrophie amygdalienne par la curiethérapie*, *Paris méd.*, 1923, 47, 110.

² It is important for the general practitioner to distinguish between the radiations and the emanation from radium. The radiations are given off uniformly for centuries, whereas the emanation, which is collected in a laboratory, loses one-half of its strength in four days.

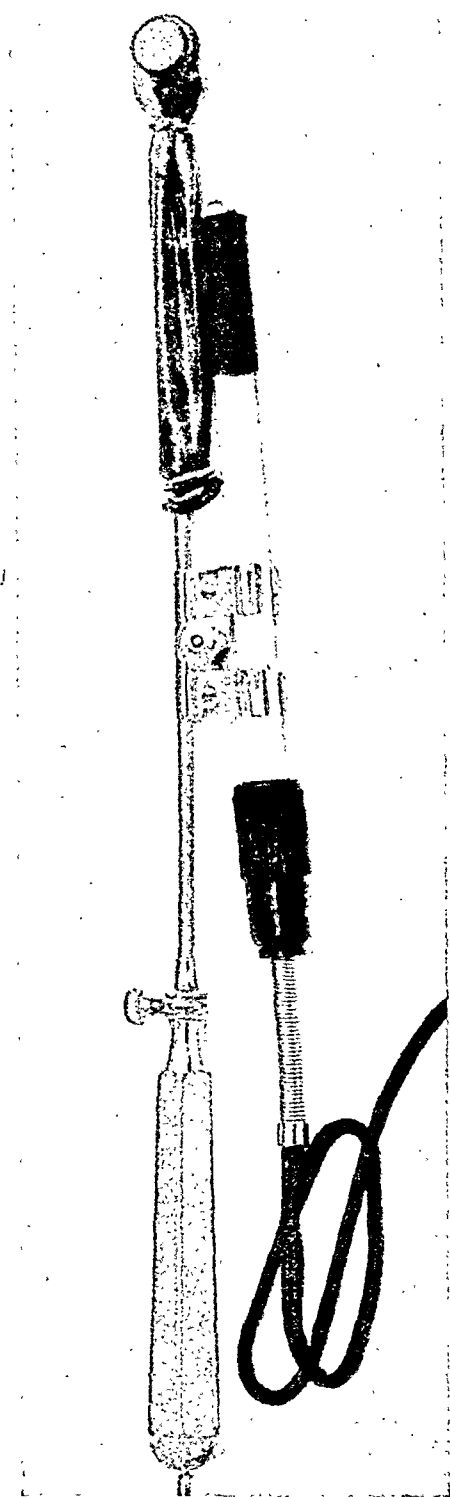


FIG. 1.—(About $\frac{1}{2}$ length.) General view of the instrument used to apply radium. At one end is the container (see also Fig. 2 C) and at the other the handle. If the screw binding the handle to the rod is set in line with the front of the container the direction of the rays issuing from the latter can be additionally noted. A rubber cot, a fresh one is used for each patient, covers the container and part of the rod and is kept in place by an elastic band at either end. The glass tube carrying the electric lamp is held firmly between double-spring clamps, designed for the purpose, bound to the rod by another clamp by turning a nut. Red rubber tubing (black is too translucent), to exclude the light, covers the lamp except at its very end. A fresh piece is used for every patient. As the lamp and the container move together, the portion of the throat to be treated and the container receive a good illumination, the intensity of which may be varied by adjusting the special rheostat (not shown in cut) which controls the lamp. The current may be turned off from the lamp by giving its hard rubber socket at the end of the wire a half-turn to the left.

does not settle to one side but remains in a thin, uniform layer.³ From the front of the container the rays spread out like an open fan, but their distribution can be controlled by diaphragms of different sizes and shapes (Fig. 2) and the amount of radiation limited and the quality modified by filters of different thicknesses. Thus the gamma rays only may be used or a mixture of the gamma and the beta rays, more properly speaking electrons, may be employed, the electrons,

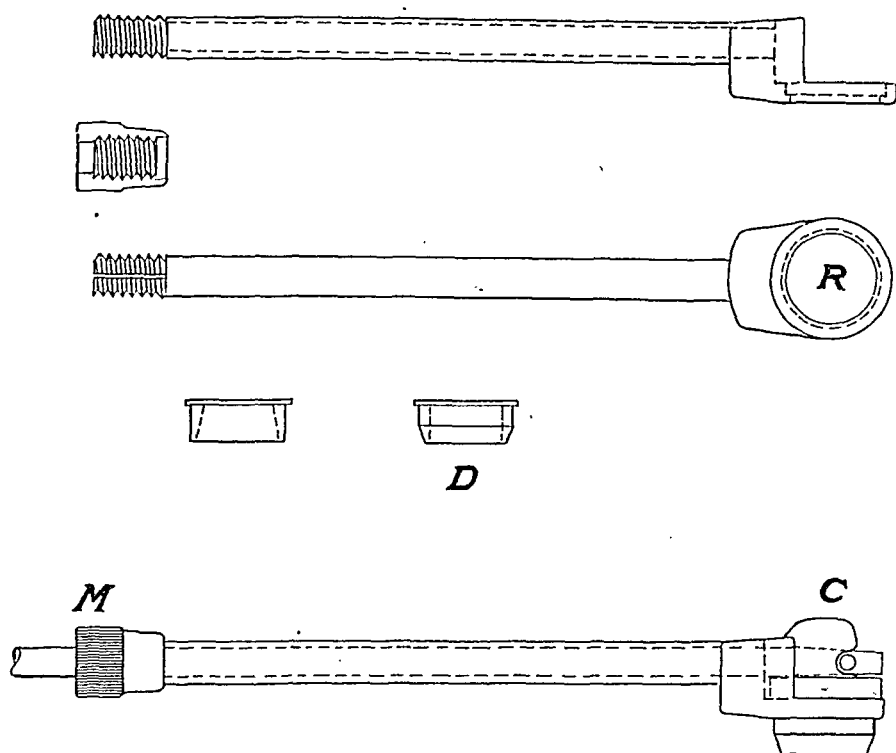


FIG. 2.—(Full size, except the tube, which is $\frac{1}{2}$ inch longer.) This figure shows the method of holding the diaphragms which may be of various shapes and sizes, as occasion requires, and two of which are shown (see *D*). The filters—not shown—are disks of aluminum, and they and the diaphragms are held in the ring *R*. This ring also acts as a large diaphragm to prevent too much spreading of the rays. *C* is the container, and on its left is a mass of gold, also seen to the left of *R*, which still further prevents the radiations from issuing in the direction of the handle. *M* is the nut with a milled head that clamps the split end of the tube, which carries the diaphragm and the filter, to the rod, at the end of which is the container. To fasten the container securely to the rod a ring of wire about 10 mm. in diameter, $\frac{1}{4}$ part of which has been cut off, is passed through the small hole on the rod (shown below *C*) and then folded back onto the top of the container. To change the filters or the diaphragms, the handle and clamp must be taken off the rod. Failure to confine the action of the radium to the tonsils by an appropriate diaphragm would give rise to irritation for a time in adjacent parts, in the pillars, for example. When the radium is to be used in the upper part of the pharynx, a higher diaphragm than that shown at *D* should be employed, in order to protect the soft palate. When the container is not in use its front is covered by a thick disk of gold held in the ring *R*.

³ I wish to express my thanks to Prof. Frederick G. Keyes for his kindness and resourcefulness in having these conditions fulfilled.

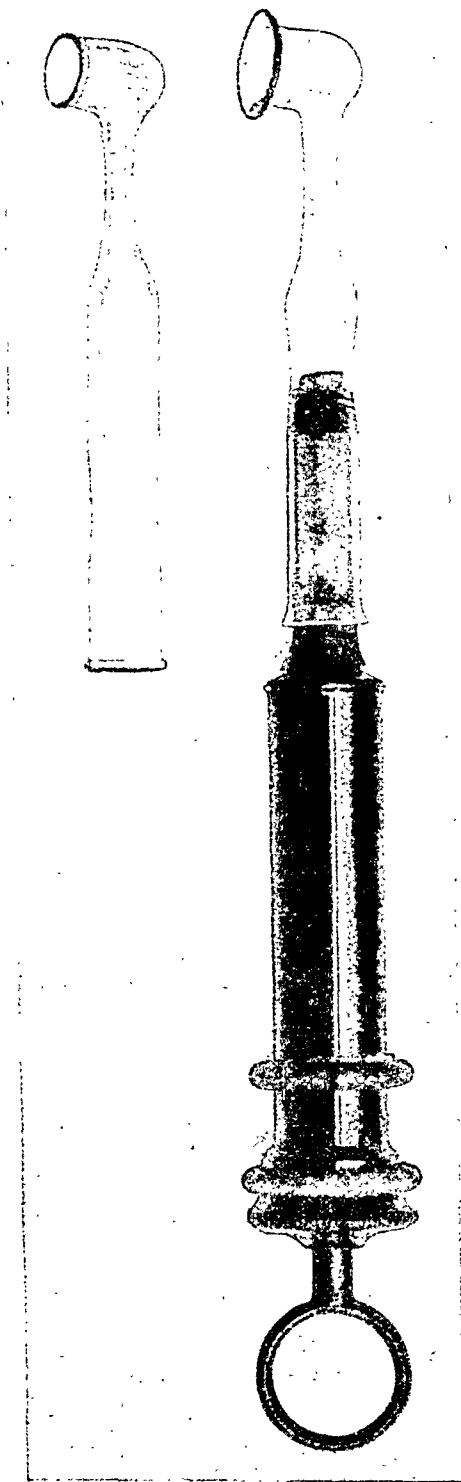


FIG. 3.—(Two-thirds size.) This figure shows an evacuator used to find out whether or not there is anything in the tonsil that can be drawn out. It consists of a hard-rubber $\frac{3}{4}$ -ounce (25 cc) syringe, the piston of which slides easily. In order to make an air-tight joint between the glass tube and the syringe the tube has been thickened about 1 inch from the end, thus its caliber has been made a little smaller. A piece of pure rubber tubing covers the entire nozzle of the syringe. After this tubing has been moistened the nozzle of the syringe is pushed gently into the glass tube a little beyond the first constriction, where it is held firmly like a cork in a bottle. The diameter of this tube just below the cup, as shown in the figure, is too small. The cup may have openings of different sizes and shapes—oval as well as round—to fit a given tonsil. The glass tube can, of course, be thoroughly sterilized. It should not be left on the syringe after it has been used, as if left it might become too firmly attached.

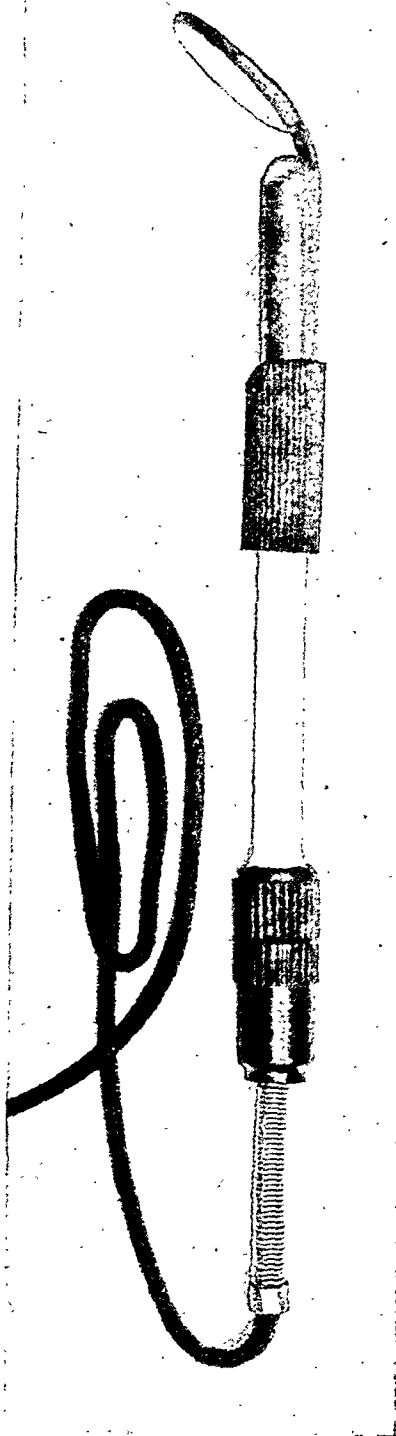


FIG. 4.—The laryngeal mirror. The backing of the mirror is of pure silver and there is no paper between the silver and the mirror. Opposite its lower portion is an electric lamp, covered for a short distance, except at the very end, with a pure silver tube split lengthwise, which is continuous with a broad band of pure silver attached to the back of the mirror. The heat from the electric lamp is conducted by this silver tube to the silver backing of the mirror, and thus the latter is kept at such a temperature that moisture from the patient's breath is not condensed on it while the laryngeal examination is going on. It is necessary that pure (not sterling) silver be used, otherwise the conduction of heat from the lamp to the mirror would be insufficient. A piece of red rubber tubing, pulled back in order to show the silver tube underneath, is cut off at one end at an angle of 45 degrees, in order to obstruct as little as possible the observer's complete view of the mirror. At the other end of the lamp there is a socket and cord attachment.

when so desired, being in such a large proportion as to make the amount of the gamma rays negligible. As the electrons have different degrees of penetrating power and the less penetrating ones are in larger proportion, the latter must be shut off by a suitable filter when the deeper tissues are to be acted upon, otherwise the tissues near the surface will receive too much radiation. The so-called alpha rays need not be considered, as they are prevented from escaping by the cover of the container. When the container is to be used for other purposes than the treatment of the faucial tonsils—lingual tonsils, for instance—it should be taken off the straight rod (shown in Fig. 1) and attached to a rod that has been bent, about 1 cm. from the end, to the angle best adapted for allowing the rays to reach the given part. The container is usually held directly against the faucial tonsil, but when used for treating adenoids, lymphoid tissue in the pharynx,⁴ the lingual tonsil or the region near the Eustachian tube, for example, it should be held near but need not touch them. The two containers I generally use hold 26 and 38 mg. of radium element respectively.

Electric Lamp. The electric lamp (Fig. 1), which gives a strong light, is covered near the end by a piece of red rubber tubing (black is too translucent), which excludes the light except at the very end where it is needed and is clamped to the rod carrying the container. The lamp and the container move together, and both the container and the portion of the throat to be treated receive a good illumination, the intensity of which may be varied by adjusting the rheostat that controls the lamp.

Evacuator. This instrument (Fig. 3) is used, if pressure is not sufficient, to see whether or not anything that it is desirable to get rid of can be drawn out of the tonsil.

Laryngeal Mirror. This mirror (Fig. 4) may be first warmed by holding it over a lamp, but after being put into the throat the electric lamp attached to it keeps it warm enough to prevent the condensation of moisture on its surface from the patient's breath, but at the same time not warm enough to be uncomfortable for the patient. The backing of the mirror and the tube surrounding the upper part of the lamp and the broad band connecting the two are of pure silver (the conduction of heat would not be sufficiently good if the silver were only sterling) and there is no paper between the silver and the mirror. I have found it useful for examining lingual tonsils and the larynx.

Tongue Depressor. Figure 5 shows a common form of tongue depressor with an electric lamp attached, the light from which is excluded except where it is desired. If a broader tongue depressor

⁴ When treating lymphoid tissue on the walls of the pharynx the aluminum cover (0.29 mm. thick) of the container makes a suitable filter and the treatments given should be about five minutes when 38 mg. of radium element are used.

is needed the lamp may be taken off the rod, as shown in the cut, and put on the other rod.

Timing Exposures. As it may be necessary to interrupt the treatment—to allow the patient to swallow, for instance—a stop watch, such as is used in football games, is useful as it permits the total length of the treatment to be accurately registered.

Treatment (Fig. 6). The treatment may be so moderate as to produce no discomfort in the tonsils or so vigorous as to cause some irritation there for a few days. There may be reasons, especially from the patient's point of view, for choosing one or the other of these ways. When 38 mg.⁵ of radium element are employed, about

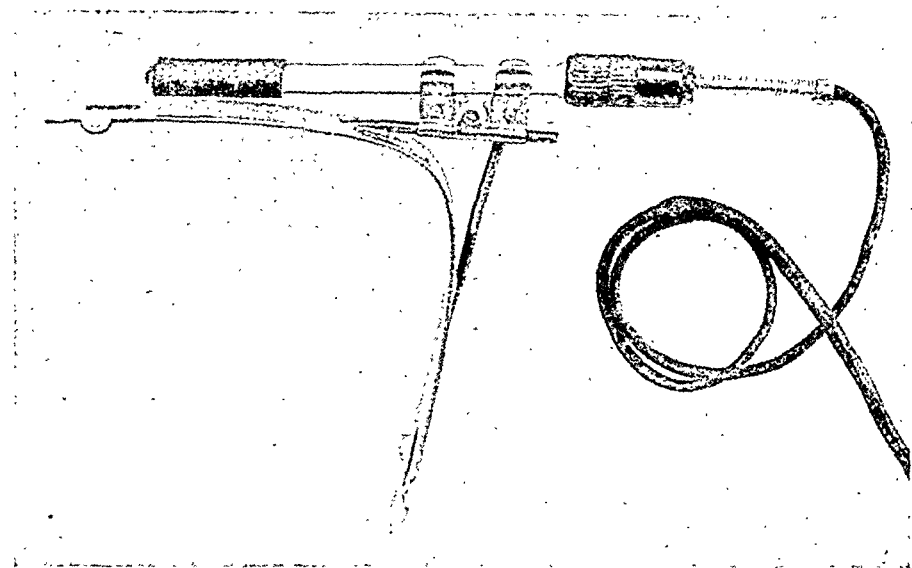


FIG. 5.—A common form of tongue depressor, with attachment for holding an electric lamp, the light from which is excluded except in the direction of the object it is desired to examine. If a broader tongue depressor is needed the lamp may be taken off the rod, as shown in the cut, and put on the other rod.

ten minutes for each tonsil, with a filter of aluminum 0.58 mm. thick, is a good first dose for an adult; a somewhat longer exposure may be given if the filter is 0.87 mm. thick. Subsequent doses should be smaller or larger as the conditions require, usually not exceeding fifteen to twenty minutes, the average number necessary being about four treatments, when aluminum filters 0.58 mm. or 0.87 mm. thick are employed, given ordinarily at intervals of about three to four weeks. If the same amount of radium element and the same filter and diaphragm are employed and the same length of exposure made, a given dose may be repeated with exactitude.

⁵ With the experience I have now had in the treatment of tonsils, I feel justified in using a larger amount of radium with the object of shortening the length of each treatment and the duration of the whole treatment.

Conditions vary widely in different patients, therefore the amount and quality of the radiations to be applied can be determined only by experience, and with this as with every new method care should be taken not to carry the treatment too far. In cases where the tonsils are very large a longer treatment than is necessary for the average case is desirable. A day or two after such a treatment, instead of the ordinary discharge a profuse one that may last for several days may follow, and the throat may be sensitive for a few days when cold, hot or highly seasoned food is eaten. The com-



FIG. 6.—This cut shows a patient reclining comfortably in a Morris chair. With the back at the angle shown in the figure the position of the patient affords the physician an excellent view of the throat and is convenient for the application of the radium. Further, in this position the saliva does not readily collect in the mouth. The seat of the chair, with its cushion, is 19 inches from the floor; if the patient is very tall, a cushion on the arm of the chair, under the elbow, may be desirable for the person applying the radium.

pensation for this is, as a rule, more rapid reduction in the size of the tonsils. Treatment should be continued while anything can be brought out of the tonsils by pressure or by the evacuator.

A good initial dose for children when 38 mg. of radium element are used, the aluminum filter being 0.58 mm. thick, is ordinarily five to ten minutes for each tonsil. For delicate children one treatment of even five minutes to each tonsil may produce such

improvement in their general condition that they will gain in strength and appetite, although there may not be much change apparent in the tonsils.

Should it be required, a freshly made 2 per cent solution of cocain may be used to desensitize the throat; or a large dose of bromides may be given some hours before the treatment, but this I have seldom found necessary. Patients have been instructed, if they have any discomfort after treatment, to use as a gargle a level teaspoonful of salt in a tumbler of water. During the stage of discharge, to obtain bactericidal action some non-caustic hypochlorite, such as chlorazene (about $\frac{1}{10}$ per cent solution) may be employed. Irritating applications such as argyrol, nitrate of silver, or the tincture of iodine should be avoided.

The 105⁶ cases considered in this paper include 4 cases of lingual tonsils, and 101 cases of faucial tonsils that are divided into the following groups:

Enlarged tonsils	10
Tonsillitis	26
Tonsillitis and arthritis	17
Arthritis	14
Miscellaneous	21
Tonsillectomy (previous)	10
Tonsillotomy (previous)	3
	<hr/>
Total	101

Enlarged Tonsils. The tonsils of these 10 patients have been reduced in size in varying degrees from one case in which there was but little tonsil left, to another in which there was great diminution in the right and some reduction in the left tonsil. This patient has had fewer colds since he had radium treatment.

W. A., aged three and a half years, was given three treatments to the right tonsil, with 38 mg. of radium element, the aluminum filter being 0.58 mm. thick, on December 16, 1922, and January 5 and 25, 1923, of five, five and seven minutes, respectively, and to the left tonsil on the same dates of five, five and eight minutes, respectively. On February 9 the tonsils could scarcely be seen; appetite had improved and she had gained 7 pounds. On April 4 she had one more treatment of eight minutes to each tonsil. When last seen, May, 1923, she was doing well. There was still something left of each tonsil.

April, 1924, her mother reported that she had improved very much.

T. L. E., aged thirty-one years, had very large tonsils and the cervical lymph nodes on both sides were affected. January 7, 1922,

⁶ It is of interest to note that a considerable number of these patients were physicians, surgeons or members of their immediate families, or nurses.

a treatment of fifteen minutes was given to each tonsil with 26 mg. of radium element. Two days later the patient could swallow more easily. When seen again, on January 13, the tonsils and lymph nodes had diminished and there was some discharge from the crypts. February 9, the lymph nodes were no longer palpable; a second treatment of twelve minutes was given to each tonsil. No further treatment has been necessary.

Tonsillitis. The size of the tonsils has been reduced in the 26 cases giving a previous history of tonsillitis. When last heard from there had been no recurrence in 21 of these cases since radium treatment was begun. In the first and second of the remaining 5 cases the treatment was at first inadequate, and a recurrence taking place, further radium treatment was given. The first has had no second recurrence; the other had a slight attack ten months later, in August, 1923. The third patient, who had enormous tonsils, had an attack of tonsillitis during treatment, when the tonsils were partially reduced, following a long automobile ride on a chilly, windy spring day when she wore no hat. She was treated during the acute stage and improved more promptly than she had previously done from the attacks to which she had been subject at not infrequent intervals for years. The fourth case (W. J.) is given on page 28. The fifth case, that had a history of tonsillitis on the left side, was one of the early cases and was first treated with radium in March, 1921, and received less treatment than I now give. In October, 1923, a recurrence took place, but the attack was much lighter than those she had had before the use of radium and lasted only three to four days instead of a week or more.

A. J., aged twenty-seven years, had a history of repeated attacks of tonsillitis. The right tonsil was treated for fifteen minutes with 26 mg. of radium element on July 29 and August 27, 1922, respectively, and the left tonsil for fifteen minutes on July 29 only. There has been no tonsillitis during or since treatment.

H. C. H., aged twenty-five years, had a history of attacks of tonsillitis for years; the right tonsil extended one-half inch beyond pillars, the left a little beyond pillars. Three treatments were given to the right tonsil, one with 26 mg. and two with 38 mg. of radium element on May 24 and November 3 and 21, 1922, of ten, eight and eight minutes respectively, and two to the left tonsil, one with 26 mg. and the other with 38 mg. of radium element on May 24 and November 3 of the same year of ten and eight minutes respectively. April, 1924, he has had no tonsillitis since the first treatment was given.

I. W. H., aged twenty-six years, had a history of tonsillitis, with tonsils swollen, and a discharge for years, and has had poor health.

Three treatments were given to the right tonsil with 26 mg. of radium element of ten, five and ten minutes on February 24, March 13 and April 5, 1922, respectively, and two to the left tonsil of ten minutes each on February 24, and April 5, 1922, respectively. On April 8, the tonsils were well behind the pillars. On April 18, the patient had a severe cold in the head, but no tonsillitis with it.

Patient has greatly improved since the application of radium to the tonsils, and had had no return of tonsillitis when last heard from.

E. S. B., aged thirty-four years, had a history of tonsillitis every winter. The right tonsil was on a level with the pillars; the left extended three-sixteenths of an inch beyond the pillars. Four treatments were given to the right and eleven to the left tonsil in 1922 and 1923, the last on March 9 of the latter year. On March 30, the tonsils were found reduced in size. The patient has had no further trouble with them and is greatly improved in health.

February, 1924, there had been no return of tonsillitis.

W. J. History of one attack of tonsillitis yearly in February. On January 5, 1922, the patient was given a treatment of fifteen minutes to each tonsil with 26 mg. of radium element, and did not have the usual February attack. On April 19 she had a second treatment of ten minutes to each tonsil. Her work prevented her from keeping the further appointments given her, and I have been told that tonsillectomy was done in 1923, following an acute attack of tonsillitis.

Tonsillitis and Arthritis. There has been improvement in the general condition of these 17 patients and they have had no attacks of tonsillitis since radium treatment was begun with the exception of 1 patient. He had a slight recurrence three years after his first radium treatment and was again treated with radium. Relief from arthritis was obtained to a greater or less extent in all these cases; in 1 case there was entire relief from pain for seven months and then a recurrence took place (the patient failed to report four months earlier as directed), which yielded to further treatment (see Case H. M. A., page 30). In another case the temporary relief after radium was followed by another attack of arthritis, which suggests, judging by experience, that some other source than the tonsils should be searched for. The following case, given in a previous paper, is illustrative.

Miss Z. had recovered from an attack of arthritis but had an acute tonsillitis when I gave her radium treatment. After one application the tonsils were reduced to a very small size and she recovered from the tonsillitis. Four weeks later the patient had another attack of arthritis, a severe one, and tonsillectomy was

done without my being consulted, the small size of the tonsils facilitating the operation. In less than three weeks after this operation she had another attack of arthritis which was followed by still another in about four weeks. An x-ray examination was made at this time which showed abscesses around two of the teeth. The teeth were removed and three months later, when last heard from, she had had no further attacks of arthritis.

T. S. W., aged fifty-six years, had had sore throats for forty years, and tonsillitis perhaps a half-dozen times in his life. He had had an attack recently, which was followed by arthritis in knees that is diminishing. Five treatments were given to each tonsil, two with 26 and three with 38 mg. of radium element, the first on May 16, 1922. Subsequently he had a cold, neuritis, pharyngitis and laryngitis, but no tonsillitis. The right tonsil is below the pillars, with a flat surface; the left tonsil is on a level with the pillars. The arthritis is diminished.

F. G. K., aged twenty-one years, has a history of tonsillitis and has had considerable trouble with her feet, which is probably due to a mild arthritis. She has been advised by several physicians to have tonsillectomy done. The right tonsil is one-quarter of an inch and the left one-eighth of an inch beyond the pillars. Eleven treatments, the first on October 3, 1922, were given to the right and five to the left tonsil. The arthritis began to clear up after the first treatment, and she took off her arch supporters and has not worn them since. She has had no tonsillitis since radium treatment was begun. The right tonsil is flat; of the left, little remains.

K. F., aged forty-seven years, has had arthritis of the upper spine and occasional attacks of tonsillitis (a mild attack during winter of 1921-1922). In December, 1921, she had intestinal influenza, followed by arthritis of the knee, which was in splints for weeks. She used a wheeled chair, then crutches and now a cane. The tonsils are slightly beyond pillars.

April 22, 1922, she was given the first treatment, ten minutes to each tonsil, with 26 mg. of radium element, and reported three days later that she felt better. The second treatment, nineteen days afterward, was given to the left tonsil only. A week later her knees were better; she could walk better, go down stairs, and turn her head more easily. On June 29 the patient could go without a cane part of the time and her knee did not trouble her unless she exercised too much. She reported, "I have not had a particle of discomfort from the treatment, not even a scratchiness in the throat, as I might have had from a cold." Treatment was interrupted during the summer, then five more treatments were given to the right and four to the left tonsil.

Her general condition is very much improved and she is able to

go without a cane except when she walks on very rough places. The tonsils are apparently very small, behind pillars. April, 1924, she has had not tonsillitis since the beginning of treatment.

H. M. A., aged forty-two years, a district nurse, has had a history of repeated attacks of tonsillitis. She has had many colds and sore throats; and her throat was swollen and hoarse practically during the whole winter of 1921-1922. She recently has had pain in finger-joints and arm. She can get through her day's work, but is tired at night. Both tonsils three-eighths of an inch beyond pillars.

On May 11, 1922, she was given one treatment of ten minutes to the right tonsil and two of ten minutes each to the left tonsil on May 11 and 25 with 26 mg. of radium element. June 6, she reported great improvement in her health and strength and that she felt much younger. "I would not know anything had been done to my throat." She had no pain whatever in joints, elbows or fingers. She failed to report in September, as directed, because she felt perfectly well. On January 4, 1923, she had an attack of acute arthritis in her left elbow; the next day it was so swollen, painful and hot that she could not use her arm for telephoning. On January 5 she was given a treatment of fifteen minutes to each tonsil with 38 mg. of radium element, the aluminum filter being 0.58 mm. thick. On the 6th she was able to use her arm, comb her hair and dress herself. Further treatments with 38 mg. of radium element were given her, five to the right and seven to the left tonsil.

April, 1924, nearly two years since her first treatment, the patient reports that she has had no arthritis since the attack of January 4, 1923, and no tonsillitis since radium treatment was begun.

Arthritis. The arthritis diminished or disappeared in these 14 cases. Radium treatment may properly be given for alleviation as well as in the hope of permanent relief, or as a test if there is a doubt as to the origin of the arthritis. It may also be used as a test in other cases in which the diagnosis is obscure, but where the tonsils might be suspected, but in which tonsillectomy would not be justified. In acute arthritis improvement is often very prompt; in subacute and chronic cases it of course takes place more gradually. It is well to bear in mind that tonsils should not be disregarded as a source of arthritis because apparently they are not enlarged or because they are submerged.

C. E. F., aged forty-seven years, has always been very nervous and has had three nervous breakdowns. She has arthritis in hands, ankles and other joints. The tonsils are within the pillars, both apparently very small, but there is some discharge from the tonsils. On October 5, 1922, the first treatment of ten minutes to each tonsil with 26 mg. of radium element was given. On October 20, she reported that the arthritis was much diminished; there was no pain

in ankles or hands; appetite was improved; and a second treatment of ten minutes to each tonsil with 38 mg. of radium element was given. On October 26, arthritis was practically gone; she felt much better; and had been able to walk more during the past week than for the past two years. On November 21 felt fifteen years younger; and had no arthritis; a third treatment of five minutes to each tonsil with 26 mg. of radium element was given. On December 15 and 29 a fourth and fifth treatment, of eight and twelve minutes, respectively, was given to each tonsil with 26 mg. of radium element. January 5, 1923, the arthritis is gone absolutely. She has lost her extreme nervousness. Both tonsils are apparently very small. March, 1924, she is still free from arthritis.

M. C. D., aged fifty-seven years, has had neuritis for some time; and arthritis for ten days in right wrist. The tonsils are apparently rather small, well within the pillars. Two treatments were given to the right and left tonsils on October 21 and November 15, 1922, of ten and five minutes, respectively, with 38 mg. of radium element and a third treatment to the left tonsil on January 20, 1923, of ten minutes with 26 mg. of radium element.

The swelling began to go down and the arthritis was relieved within twenty-four hours. On January 26, 1923, no tonsil was visible, even when the plica was pushed aside. There was no arthritis or neuritis when last heard from.

P. F. had arthritis in feet, ankles, hands and wrists. The right tonsil was enlarged in its lower part, a little in front of the pillars. She has had treatments at long intervals, the first May 29, 1922, 10 to the right and 9 to the left tonsil in all, and has been greatly relieved.

This patient has been under direct observation; has gained steadily and now gets about her work without the great difficulty that she formerly had.

Miscellaneous. The tonsils of these patients, 21 in number, were treated with radium with satisfactory results, for a variety of causes, such as frequent colds, the relief from which was very striking, sore throats, sensitive throat with pain in the ears, neuritis and pain in the throat.

L. M. History: The patient cannot breathe through the nose; she has had an itching sensation in the throat for one or two years and colds all the time; the tonsils are within the pillars; the pharyngeal wall is rough.

November 14, 1923, a treatment of fifteen minutes was given to each tonsil with 38 gm. of radium element, the aluminum filter being 0.58 mm. thick, and a treatment of seven minutes to the pharynx, the filter being 0.29 mm. thick. December 6, she felt

better, the tonsils were smaller and were well within the pillars; a second treatment of fifteen minutes was given to each tonsil. January 8, 1924, she had a good appetite and had gained in weight, no treatment was given. February 8, the tonsils were still further within the pillars; a third treatment of fifteen minutes was given to each tonsil. April, 1924, she has had no colds since the use of radium.

H. L., aged seven years. Her physician thought there was risk of mastoid trouble if the tonsils were not cared for. She had been subject to earaches. The treatments by radium were as follows: December 8, 1921, fifteen minutes to the right and nineteen minutes to the left tonsil with 26 mg. of radium element, the aluminum filter being 0.87 mm. thick; January 7, 1922, fifteen minutes to each tonsil with the same amount of radium, but with an aluminum filter 0.58 mm. thick. The patient has had no earaches since radium treatment was given.

Lingual Tonsils. In treating lingual tonsils the container should be held on a rod the end of which has been so bent that the rays issue downward and forward and should be near but need not touch the tonsil. It is not well to push the treatment of lingual tonsils as rapidly as may be done in faucial tonsils, because all the food must pass over the tongue. The discharge that takes place some days after treatment may trickle down to the trachea and cause coughing. Should this happen, relief may be had by spraying the parts with peroxide of hydrogen, as washing off the discharge stops the cough temporarily. In one case the relief from constant cough at first was very striking, but later was less marked and treatment has not been continued; in the three others there has been continued improvement. More time and cases are needed to estimate the value of radium treatment for lingual tonsils.

*Previous Tonsillectomy and Tonsillotomy.*¹ Six of the 10 patients with a history of tonsillectomy and the 3 patients with a history of tonsillotomy had tonsillitis after these operations. There has been no recurrence since radium treatment was given.

B. E. C., aged thirty-one years, had tonsillectomy performed in 1919, but has had one or two severe attacks of tonsillitis every winter since then. She was advised to have a second operation, which she declined. She had a severe attack of arthritis before radium treatment. Three treatments were given to each tonsil, on February 12, March 5 and 19, 1923, respectively, with 38 mg. of radium element, the length of the treatments varying from eight to fourteen

¹ In this connection the following statement is pertinent: "A study of more than 30,000 patients from various sources one to four years after operation shows permanent results in only about one-half of the total number." Laura A. Lane, M.D., Associate Attending Surgeon, Eye, Nose and Throat Department, Minneapolis General Hospital; Minnesota Med., 1923, vi, 97.

minutes for the right tonsil and twelve to eighteen minutes for the left tonsil.

She has had no arthritis or tonsillitis since the first treatment. The right tonsil is almost gone, except for a small tab under the anterior pillar; the lower part of the left tonsillar fossa has a considerable amount of tissue in it.

S. H. H. had tonsils and uvula operated upon when four years old. She has very little tonsillitis, but catches cold easily. One treatment of ten minutes was given to each tonsil on February 1, 1922, and a second treatment of five minutes to the left tonsil on March 2 of the same year with 26 mg. of radium element.

Since radium treatment was begun she has had no tonsillitis, although she has had two colds and one attack of grippe. She feels well, better than she has ever felt. Both tonsils apparently are very small.

W. H. A., aged twenty-five years, had tonsillectomy performed in childhood, but has frequent attacks of tonsillitis. Three treatments were given to each tonsil of ten minutes each on June 10, July 13 and August 12, 1922, respectively, with 26 mg. of radium element.

The tonsils are well within the pillars. Subsequently he had a hard cold for a week, but no tonsillitis with it.

It is of interest to note that the tonsillar tissue left after tonsillectomy probably differs from that left after radium treatment. It is well to use radium before regeneration takes place.

The general condition of the patient improves, and the weight often increases after the use of radium. In a word, the whole picture may be altered by radium treatment. The patient may be changed from a tired, ambitionless individual to one with "pep," as patients often express it, and these results may be accomplished without irritation in the throat. In some cases great improvement has taken place in the general condition within two or three days before any change was apparent in the tonsils, for an explanation of this I think we must go to the biochemist, which suggests that we may do well not to lay too much stress on the necessity of their extirpation if there is improvement in other directions. How far it is desirable or necessary to reduce these organs in order to ensure no further attacks of tonsillitis, or of arthritis, of which the tonsils are the source, is yet to be determined. In nearly all these cases the tonsils have been reduced in size, but as a rule their complete removal has not been attempted. In some cases, after the treatment was completed, no tonsil was seen when a curtain, the edge of which was directed backward and which was attached near

the top of the anterior pillar and reached to near the base of the posterior pillar, was drawn aside; but when the finger was passed around the curtain, a flattened mass about as large as a good-sized pea was felt near the anterior pillar on the side toward the cheek. In such cases I should not expect that there would be any further trouble, but when the tonsils are not so reduced it remains to be seen after how long an interval, if at all, trouble will occur. Three of the 88 patients that make up the first five groups (the other 13 patients had had tonsillectomy or tonsillotomy before radium treatment was given) had tonsillectomy after radium treatment. The tonsils in the first case were large and fibrous, radium is not adapted to getting rid of the fibrous portion of a tonsil, and were removed for mechanical reasons; the tonsils in the second case were greatly reduced in size by radium treatment, but the patient had a sensation of something in his throat that caused him to swallow continually—I have not yet been able to learn whether or not his condition improved after tonsillectomy; the third patient, before radium treatment was completed (see W. J., page 28) had an acute attack of tonsillitis and tonsillectomy was done.

Conclusions. Radium is a valuable therapeutic agent not only for the treatment of faucial tonsils, but also for other lymphoid tissue in the throat.

The output of the radiations from radium is uniform in quantity and quality, therefore the dosage can be accurate; if the radiations used in a given case are adapted to the conditions present this remedy is an unusually safe one in careful hands.

This method of treating the tonsils with radium, so far as can be determined by an experience of over three years, evidently has advantages:

For cases that are not good operative risks.

For those in which tonsillectomy is incomplete, instead of a second operation.

For some cases in which the diagnosis is obscure.

In how large a proportion of the cases, for which tonsillectomy is ordinarily advised, radium should be used, time and further experience will demonstrate.

This method is also adapted to the treatment of lymphoid tissue in the pharynx and in the region near the Eustachian tube in cases of ear trouble.

There need be no delay in the use of radium on account of the season of the year, or because of acute conditions in the tonsils themselves, or of an acute stage in diseases that have their source in the tonsils.

There have been no harmful results from the use of this method in the more than 200 cases that I have treated, the first of them more than three years ago.

LIPOIDS IN 1000 DIABETIC BLOODS, WITH SPECIAL REGARD TO PROGNOSIS.

BY H. GRAY, M.D.,

BOSTON.

(From the Clinic of Dr. E. P. Joslin at the New England Deaconess Hospital, Boston.)

THE first anxious demand of the patient who has just been told that he has diabetes is apt to be: "What is the outlook, doctor? I want to know the truth." Very often a reliable reply could be offered only by a few physicians of special experience and acumen. For the rest of us who are treating the majority of the nation's million diabetics, reliance must be based on facts and more facts. Figures on the fat in the blood are strewn through case reports in the literature, but for practical guidance there is real need of a crystallization. It is most regrettable that the records of 10,000 lipid analyses by Miss Mary Wishart¹ were lost during the war, since these with Dr. F. M. Allen's² clinical data on the same patients, might well, when critically digested, have thrown more light than can this series, which when subdivided yields groups often too small for entirely satisfactory numerical results. Two at least of the findings, however, justify this communication: (1) Diagnosis: The blood fat was abnormal with nearly the same constancy as was the blood sugar. (2) Prognosis: Most long-lived diabetics showed a blood fat less than 1 gm. per 100 cc.

Material. In the six years that have elapsed since my last study on blood lipoids in this clinic,³ the value of the subject matter has been enhanced, in that a considerable number of cases have been closed by death, and the series has been enlarged by many new cases both completed and living. Of the total number of patients studied here, the proportion alive on June 1, 1923 was 71 per cent. The great bulk of observations were made before the advent of insulin. The observations will now be discussed under the same headings as formerly.

Definitions. As before, the term lipoids is used to cover any or all fatty substances: fatty acids, cholesterol, lecithin. Blood fat means those substances measured by Bloor's method⁴ for so-called "total fat," namely, fatty acids plus total cholesterol but not lecithin.

Blood fat in whole blood will be the chief chemical analysis discussed in reference to each clinical aspect; in addition, under prognosis, cholesterol will be considered, both in whole blood and plasma.

The time of taking the blood samples was generally before breakfast, and also in general before the beginning of insulin treatment; the exceptions do not seem worth individual attention at present.

The first conclusion offered in the former paper was that the most satisfactory single determination for following a diabetic patient was Bloor's fat method, "total fat" as he called it, on whole blood. This method has since been depended on in this laboratory whenever a measure of the lipoids has been wanted. Done by a variety of hands, and during parts of the period done under unusual pressure of work, the results may be somewhat less comparable than those previously reported, but are believed adequate.

The notation per cent will be used so often to make prominent the frequency of occurrence of the various topics under discussion, that I believe clearness will be furthered by refraining from expressing chemical results in per cent. The biological chemists today appear to favor the notation mg. per 100 cc, but some have used gm. per 100 cc, and as this permits us to keep the decimal point in the same place as when saying per cent, this notation will be used throughout the paper.

There were 1062 blood samples, from 588 patients. The tables below will present sometimes the total of admission and later values consolidated, other times only admission values; sometimes figures from both living and fatal cases, other times from completed cases alone.

Relative Frequency of Various Levels of Blood Fat. First, let us recollect the highest normal blood fat reported:⁴ 0.67 gm. per 100 cc. Now among our diabetics the commonest level was 0.7 to 0.8, occurring in 14 per cent of the blood samples, while in 60 per cent of the blood samples, the level was less than 1, and in 90 per cent less than 1.5 gm. per 100 cc. Higher levels occur with decreasing frequency, until we see that values of 1.8 or more occurred in only 7 per cent of the samples (Table I). These exceptional cases might repay special study.

Diagnosis of Diabetes from the Blood Fat. Particular attention was invited in the former paper to the regularity with which diabetes was accompanied by increased blood fat. There the values exceeded the normal maximum (0.67 gm. per 100 cc) 93 per cent of the time. In the present series abnormal blood fat was found in 78 per cent of the 1062 specimens, versus abnormal blood sugar (more than 0.11 gm. per 100 cc) in 72 per cent of the same specimens. If only the initial values be examined, the corresponding constancy of abnormal blood fat was 76 per cent, of blood sugar 82 per cent of the 588 patients. In making this count the blood sugar has been given the benefit of every doubt, because whenever the record was not clear as to whether the blood had been taken fasting, that has been assumed the case. This assumption is believed to favor the blood sugar because it is in general more markedly affected than the blood fat by a single meal. Conclusions that may be drawn are accordingly: On admission the blood sugar was abnormal somewhat more uniformly than the blood fat, but the reverse was true

after treatment. For diagnosis, therefore, the blood fat seems to be only slightly inferior to the blood sugar in untreated patients, and in treated cases somewhat superior. This greater stability of the blood fat at all events is worth consideration, even by those who still believe the more labile blood sugar to be more valuable.

TABLE I.—FREQUENCY OF VARIOUS LEVELS OF BLOOD FAT.

Blood fat, gm. per 100 cc.	No. of analyses.	All analyses, per cent.	
9.55	1	0.1	7.2
8.90	1	0.1	
7.04	1	0.1	
6.30	1	0.1	
5.00	2	0.2	
4.00	3	0.3	
3.00	8	0.8	
2.90	3	0.3	
2.80	1	0.1	
2.70	6	0.6	
2.60	4	0.4	
2.50	4	0.4	
2.40	4	0.4	
2.30	8	0.8	
2.20	8	0.8	
2.10	2	0.2	
2.00	9	0.8	
1.90	2	0.2	
1.80	8	0.8	
1.70	15	1.4	
1.60	17	1.6	
1.50	31	2.9	
1.40	29	2.7	
1.30	25	2.4	
1.20	53	5.0	
1.10	64	6.0	
1.00	103	9.7	
0.90	111	10.4	
0.80	139	13.1	
0.70	149	14.0	
0.60	122	11.5	
0.50	74	7.0	
0.40	38	3.6	
0.30+	16	1.5	
Total	1062	100.0±	

Dead Diabetics with Normal Blood Fats. With a normal admission blood fat yet now dead, there were 28 patients. Only 2 were mild, and they died of cardiorenal disease; 7 were of moderate severity; 19 were severe despite the low blood fats; 14 of them died in coma. In these 14 the interval between the blood fat and death was: Less than one year in 8, between one and two years in 5, and four and a half years in 1 case.

For the whole group of 28, the average interval between the normal blood fat and death was only 1.3 years. The average weight at the time of the fat analysis was 20 per cent under the normal standard. These last two facts again indicate that diabetes may

be severe despite a normal fat level. The best explanation that I can offer for the paradox is the submaintenance régime on which these patients presumably had been living prior to the blood analysis, a presumption suggested by the average dietary fat (known for 15 of them), namely, only 0.6 gm. per kilo, and the rather low blood sugar of 0.21 gm. per 100 cc.

To prove this explanation we need more observations on patients seen frequently over a period of years.

Duration of Disease before Blood Fat. The longer the duration the lower the average blood fat, as shown before,³ and as confirmed by the amplified figures in Table II. The explanation offered is that patients who store up high blood fat are too severe to live long. The facts in Table II may be insisted on because they seem precisely contrary to the statement in the literature that the more long-standing the diabetic condition the more marked the abnormality in the blood lipoids.⁴

TABLE II.—DURATION OF DIABETES BEFORE BLOOD-FAT ANALYSIS.*

Duration, years.	No. of analyses.	Blood fat, average gm. per 100 cc.	
Under 1	49	1.01	} 1.26
1 to 1.9	43	1.31	
2	21	1.60	
3	5	1.89	
4	9	0.92	} 0.97
5	10	1.03	
6	14	0.95	
7	4	0.86	} 0.80
8	4	0.87	
9	2	0.92	
10	15	0.83	
20	4	0.72	
<hr/>		180	

Prognosis. Can life expectancy be foretold from the blood-lipoids? An answer was sought in 1917 by an elaborate tabulation, but with scanty results owing to the short interval since the patients' discharge from hospital. A concrete reply has been achieved recently by Rémond and Rouzaud.⁵ They found among 189 diabetics that 7 per cent had a plasma-cholesterol of 0.3 gm. per 100 cc or more, and that of these cases again only 7 per cent survived after the findings as long as two years. Their cholesterol danger line (Grigaut's technic⁶) corresponds to 0.43 gm. per 100 cc by Bloor's method, as nearly as I can judge from the average normals given by the authors of the respective methods: Grigaut 0.16 gm. per 100 cc and Bloor 0.23 gm. per 100 cc. Furthermore, it may be

* Unselected group of 180 specimens, admission and later, from both living and fatal cases.

well to remind ourselves that the highest cholesterols among the 20 normal bloods published by Bloor were 0.31 gm. per 100 cc on plasma and 0.25 gm. per 100 cc on whole blood. These explanations will help us now to understand certain of the groupings in Chart I

CHOLESTEROL g /100 cc.	LENGTH OF LIFE AFTER PLASMA-CHOLESTEROL ANALYSIS IN YEARS								
	0.1 or less	0.2— 0.5	0.6— 0.9	1.0+	2.0+	3.0+	4.0+	5.0+	6.0+
0.31 or less	..	::	:::	:::	:::	
0.32—0.42		.	.	::		::
0.43—0.70	::		:::	:::			::
0.71—2.20			::	.					

CHART I.—High cholesterol means bad prognosis. Each dot = 1 analysis.

and Table III (for plasma), and the table recently shown elsewhere⁷ (for whole blood). These tables show that each successive group with higher cholesterol was characterized by a decided decrease in subsequent length of life.

TABLE III.—RELATION OF PLASMA-CHOLESTEROL TO PROGNOSIS.*

Plasma-cholesterol, gm. per 100 cc.	No. of analyses.	Length of life from blood analysis to death, or if alive June 1, 1923, years.
0.31 or less	64	4.1
0.32 to 0.42	15	3.1
0.43 to 0.70	38	1.8
0.71 and over (maximum, 2.2)	6	0.9
	123	

From Chart I it may be reckoned that the danger level of plasma-cholesterol was exceeded by 15 per cent of the patients, or 35 per cent of all specimens if we include both admission and later analyses; this shows the greater severity of these cases of Dr. Joslin's, as compared with 7 per cent in the series quoted.⁵ Of his ill-fated group, 31 per cent lived more than two years, thus showing a happier outcome than (7 per cent) in the series quoted.

There are a few extraordinarily high plasma-cholesterols in the literature, which may be assembled here, translated where necessary into Bloor equivalents:

1.15 gm. per 100 cc (Grigaut⁸),

1.20 gm. per 100 cc (Rémond and Rouzaud⁵),

* Blood technic, with sodium ethylate; analyses by H. G.

1.35 gm. per 100 cc (Epstein and Lande⁹),

1.67 gm. per 100 cc (Bloor¹⁰),

1.71 gm. per 100 cc (Bloor¹¹),

1.90 gm. per 100 cc (Bloor¹²),

2.11 and 2.20 gm. per 100 cc (present writer³ on Joslin's Case No. 786 on two different days about nine months before coma; the simultaneous values on whole blood were 1.48 and 1.50 gm. per 100 cc).

Converse grouping by length of life, for 115 specimens on living and fatal cases (the latter 41 per cent of the 115) shows the same results (Table IV). For example, when the patient survived less than two years, the average plasma-cholesterol was 0.53 versus 0.3 when the patient lived more than two years.

TABLE IV.—RELATION OF BLOOD-CHOLESTEROL TO PROGNOSIS.

Length of life after blood analysis to death, or, if living, to June 1, 1923, years.	No. of analysis.	Cholesterol, gm. per 100 cc.	
		Whole blood.	Plasma.
0.1 or less	6	0.38	0.48
0.2 to 0.5	6	0.25	0.27
0.6 to 0.9	16	0.59	0.75
1.0+	32	0.37	0.46
		0.41	
		0.53	
2.0+	11	0.30	0.32
3.0+	7	0.37	0.45
4.0+	2	0.25	0.28
5.0+	4	0.20	0.22
6.0+	30	0.25	0.28
7.0+	1	0.21	0.25
		0.27	
		0.30	

Prognosis from Blood Fat. Let us now return to the figures by the "total fat" method of Bloor on whole blood. Grouping the results according to the length of life subsequent to determination of the blood fat revealed little in my earlier paper but here makes plain the progressively longer expectation of life, the lower the blood fat. This rule holds whether we consider the admission values alone (patients), or both admission and later values together (all specimens).

For instance, if we group 351 specimens on fatal cases according to subsequent length of life, we find that when death occurred in six months or less, the blood fat averaged 1.15 gm. per 100 cc, when death occurred in from half a year to two years, fat averaged 1.03 gm. per 100 cc, if in more than two and less than four years the blood fat averaged 0.93 gm. per 100 cc, and if in more than four years the blood fat averaged 0.79 gm. per 100 cc. A table of these figures in greater detail may be found elsewhere.⁷

Or conversely, if groups are made according to the level of blood fat, it is again obvious that the greater levels are associated with progressively shorter lives, witness the averages in Table V, especially in the last column.

TABLE V.—RELATION OF BLOOD FAT TO PROGNOSIS.*

	Length of life after blood fat, years.					
Blood fat, gm. per 100 cc.	Fatal; admission and later specimens consolidated.	Living; admission and later specimens consolidated.	Admission specimens; fatal and living specimens consolidated.	Later specimens; fatal and living specimens consolidated.	Grand total.	
0.67 or less .	(78) 1.2	(151) 2.8	(146) 2.5	(83) 1.9	(229) 2.3	
0.68 to 0.99 .	(135) 1.2	(296) 2.4	(278) 2.2	(153) 1.8	(431) 2.1	
1.00 to 1.49 .	(87) 0.9	(176) 2.1	(130) 1.7	(133) 1.6	(263) 1.7	
1.50 to 1.99 .	(26) 0.9	(38) 1.7	(24) 1.2	(40) 1.5	(64) 1.4	
2.00+ .	(4) 0.6	(27) 1.9	(12) 1.4	(19) 2.0	(31) 1.7	
3.00+ .	(2) 1.5	(7) 1.0	(2) 1.5	(7) 1.0	(9) 1.1	
4.00+ .	(7) 0.7	(2) 0.3	(3) 0.8	(6) 0.5	(9) 0.6	

(Parentheses enclose the number of specimens consolidated to obtain each average length of life.)

* Whole blood, Bloor's "total-fat" method. Highest value among 20 normal bloods (Bloor) was 0.67 gm. per 100 cc.

BLOOD FAT g/100 cc.	LENGTH OF LIFE AFTER BLOOD-FAT IN YEARS								
	0.1 or less	0.2- 0.5	0.6- 0.9	1.0+	2.0+	3.0+	4.0+	5.0+	6.0+
0.67 or less	■	■	■	■	■	■	■	■	■
0.68-0.99	■	■	■	■	■	■	■	■	■
1.00-1.49	■	■	■	■	■	■	■	■	■
1.50-1.99	■	■	■	■	■	■	■	■	■
2.00+	■	■	■	■	■	■	■	■	■
3.00+	■	■	■	■	■	■	■	■	■
4.00+	■	■	■	■	■	■	■	■	■

CHART II.—High blood fat means bad prognosis. Each dot = 1 analysis.

The frequency distribution is plotted in Chart II. Among many combinations there visible, according to one's interest, note that when a blood fat turned out to be 2 gm. per 100 cc or more, the patient lived for less than two years in 86 per cent of such observations.

A high initial blood value, for sugar or fat, provided it yields under treatment to a value fairly near normal, may be thought of small import. The evidence given here indicates that a fall in the blood figure improves the prognosis for the average patient, but it does not prove that a fall in a particular patient renders his future as favorable as that of another patient whose value never was elevated. Furthermore, it seems hardly likely that such proof can be produced. On the other hand, a closely related but not identical possibility, which would be encouraging to patients with high admission values, seems logical enough to merit future study: A patient whose blood value starts at (say) three times normal but is reduced by faithfulness under treatment to nearly normal, may have a better prospect than a patient whose blood starts at only twice normal but remains there.

Weight at Time of Blood Fat. The evidence of this enlarged series, whether we consider only admission values on fatal cases alone (table recently published elsewhere⁷), or both admission and later values on both fatal and living cases (Table VI), confirms my earlier conclusions. Patients who at the time of taking blood were overweight or normal in weight showed a moderately elevated blood-fat level, with the normal weight blood fats averaging 12 per cent higher. The underweights, meaning patients 10 per cent or more below normal standard, showed a blood fat average of 1.13 gm. per 100 cc which is 40 per cent higher than the average blood fat of 0.81 gm. per 100 cc for the overweight diabetics. In other words, severe diabetics develop high fats simultaneously with emaciation. This rather paradoxical phenomenon is worth further study, perhaps in connection with observations: (1) In carcinoma, of increased blood cholesterol¹³ (and blood sugar¹⁴); (2) in fasting, of increased blood lipoids¹⁵ and (3) conversely in obesity—of decreased blood lipoids.⁹

TABLE VI.—RELATION BETWEEN BLOOD FAT AND BODY WEIGHT WHEN BLOOD WAS TAKEN.*

Weight of patient at time of blood, expressed in per cent overweight (+) or underweight (—), compared with medico-actuarial insurance tables of average weight for height and age.	No. of analyses.	Blood fat, average, whole blood (Bloor's method), gm. per 100 cc.
+21 and over (maximum, +84)	44	0.83
+11 to 20	44	0.80
+1 to 10	82	0.94
±0	4	0.75
-1 to -10	116	0.90
-11 to -20	147	0.94
-21 to -30	153	1.10
-31 to -40	143	1.14
-41 and under (minimum, -59)	64	1.60

* All specimens, admissions and later, on both fatal and living patients.

Blood Sugar in Relation to Blood Fat. Increase of glucose in the blood is accompanied by increase of blood fat on the average (Table VII), though in individual patients a lack of parallelism is often puzzling.

TABLE VII.—RELATION OF BLOOD SUGAR TO BLOOD FAT.

Blood sugar (W. B., Folin), gm. per 100 cc.	No. of analyses.	Blood fat (W. B., Bloor), gm. per 100 cc.
0.11 and under	158	0.85
0.12 to 0.16	212	0.92
0.17 to 0.21	177	0.99
0.22 to 0.26	193	1.05
0.27 to 0.31	148	1.22
0.32 and over	104	1.16

Course of Blood Fat in Treated Diabetics. A progressive fall of blood fat under treatment, even with high fat diet, is conspicuous in Marsh's recent charts.¹⁶ In the present series, among the fatal cases which had 3 or more fat analyses, the general slant of the blood-fat curve was downward in only 56 per cent, but upward in the remainder, that is in approximately half the cases.

If a composite curve be made by averaging such blood-fat values as were taken on admission, those one week later, and so forth, we

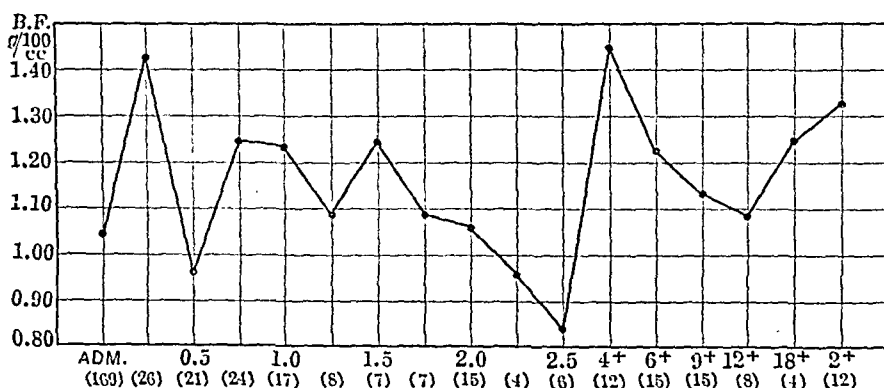


CHART III.—Course of blood fat in treated diabetics. Interval after admission, in months. Fatal cases. (Parentheses enclose number of blood fats averaged for each plotted point.)

get Chart III. The plotted averages are disappointingly irregular in distribution, very possibly because of the small number of cases represented by some of the averages. The general aspect of the curve, however, suggests the following tendencies in the behavior of the blood fat:

1. Abrupt rise consequent on beginning of treatment by severe sub-maintenance diet. This may be fundamentally related to the rise in lipoids after fasting, as noted elsewhere.¹⁵

2. Fairly regular fall during about the first three months thereafter.

3. Irregular but definite rise during subsequent life till death.

If a curve be plotted from an unusually long series of blood fats on a patient who has seemed accurate and faithful the same tendencies appear (Chart IV):

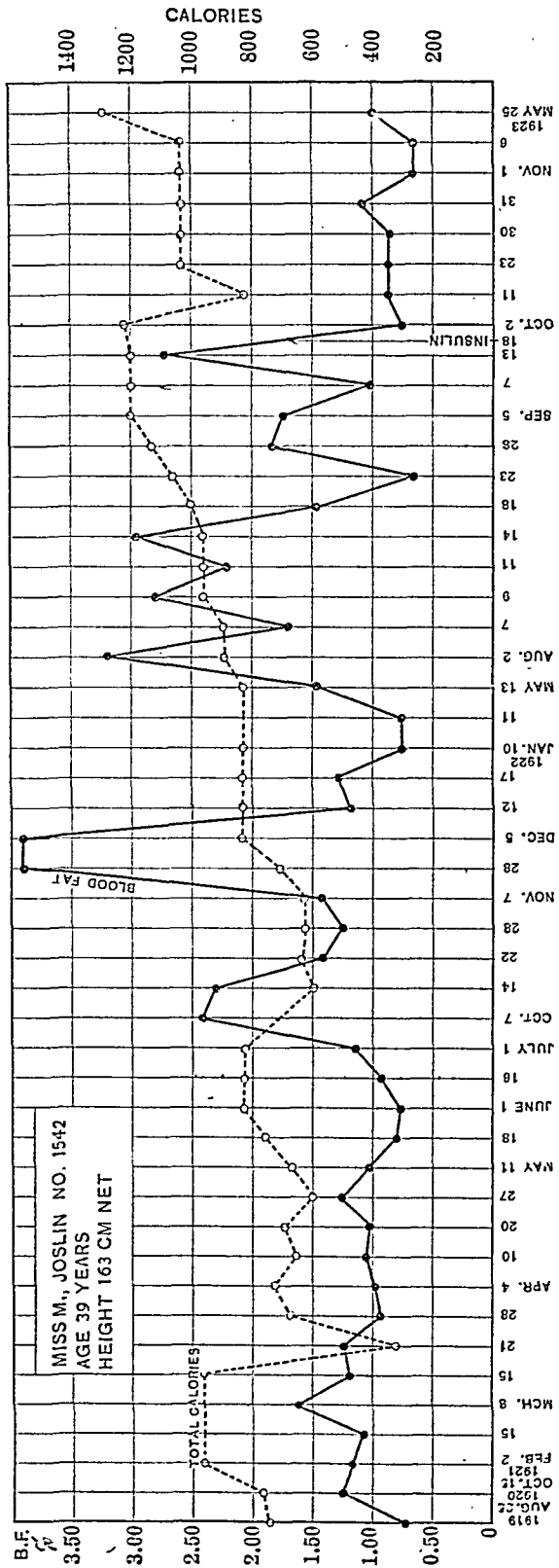


CHART IV

1. Rise at first 0.75 to 1.65 per cent, average of 5 values being 1.18 per cent.

2. Fairly regular fall later for about four months, minimum 0.8 per cent and average level for 12 observations being 1.03 per cent.

3. Irregular but definite rise during ensuing year (October 1921–October 1922); peak 3.85 per cent and average of 23 determinations being 1.92 per cent.

4. Then the advent of potent insulin produced a beautiful fall and flattening of the curve below the danger level of 1 per cent, the average for 8 analyses being 0.85 per cent. Insulin effect is the more picturesque because during this period the total calories are only a little lower than during the preceding period of severely high blood fats.

5. The astounding fluctuations during the severe stage appear to have been correctly observed, in view of the duplicates both at the highest (Nov. 28 and Dec. 5) and at the lowest points (January 10 and 11). At the same time these fluctuations can not be now explained from the recorded calories, fat, carbohydrate, or general condition of the patient. Solution seems to demand the most precise technic, together with more frequent determinations (probably daily) than hitherto usually made.

Summary. A plea is made for more use of statistics in prognosis.

The blood fat (and cholesterol) in a considerable series of diabetics is studied in regard to the relative frequency of various levels of blood fat, diagnosis, duration of disease before fat determination, duration afterward (= prognosis), body weight, blood sugar, course of blood fat under treatment.

Frequency distribution: Strikingly high blood fats are astonishingly infrequent, for example, of 1062 blood samples, 90 per cent had blood fats below 1.5 gm. per 100 cc.

Diagnosis. The blood fat is above normal with a consistency equal to the blood sugar, for example, of the 1062 samples 78 per cent had blood fats above 0.67 gm. per 100 cc, which is the high limit of normal; while 72 per cent had blood sugars above 0.11 gm. per 100 cc before breakfast, which is taken here as the high limit (if you prefer as a limit 0.12 or 0.13, the blood sugar will make a worse showing).

The diagnosis of renal glycosuria, as well as of diabetes mellitus, may be materially aided by a blood fat. Hornor¹⁷ has suggested that renal glycosuria may be ruled out whenever the blood fat is excessive, certainly if over 1 gm. per 100 cc.

The longer the duration of the disease before examination, the lower the blood fat, presumably because only those patients live long who have low fats, that is, mild diabetes.

Prognosis. Two years has been suggested as a convenient limit to use for a general statement. The cases in this series to achieve this length of life had blood fats averaging less than 1 gm. per 100 cc. When the fat exceeded 2 gm. per 100 cc, the patient lived less than

two years in 86 per cent of the instances. Detailed tables demonstrate the rule that progressively each group with a higher blood fat level (or similarly with higher cholesterol) is characterized by a distinctly shorter life expectancy.

Body weight: Underweight diabetics, that is, the severe cases of denutrition (10 per cent below standard), showed blood fats 40 per cent higher than the fat diabetics, the mild cases.

Blood sugar parallels blood fat more in averages than in individual cases.

The course of the blood fat under treatment is less easily interpreted than the blood sugar and needs further study.

All in all, blood-fat analyses are a material aid in the diagnosis and especially the prognosis of diabetes mellitus, and therefore where a laboratory is at hand deserve to be done, at least on admission of every patient.

REFERENCES.

1. Wishart, M. B.: Lipemia 1, Jour. Metab. Res., 1922, 2, 199.
2. Allen, F. M.: Lipemia 2, Jour. Metab. Res., 1922, 2, 219. (Exhaustive critical bibliography of lipoids in diabetes.)
3. Gray, H.: Blood Lipoids in 131 Diabetic Bloods, Boston Med. and Surg. Jour., 1918, 178, 16, 50, 91, 120, 156.
4. Bloor, W. R.: A Method for Determination of Fat, Jour. Biol. Chem., 1914, 17, 377. (See also other details in reference No. 3.)
5. Rémord and Rouzaud: Sur la valeur pronostique de la cholestérinémie dans le diabète, Bull. de l'Acad. de méd., 1923, 89, 60.
6. Grigaut, A.: Procédé colorimétrique de dosage de la cholestérine dans l'organisme, Compt. rend. Soc. de biol., 1910, 68, 791, 827; 1911, 71, 513; Thèse, Paris, 1913.
7. Joslin, E. P.: Treatment of Diabetes Mellitus, Philadelphia, third edition, 1923, p. 199.
8. Grigaut, A., and l'Huillier, A.: Taux comparé de la cholestérine, Compt. rend. Soc. de biol., 1912, 73, 202 (Case XV).
9. Epstein, A. A., and Lande, H.: Studies on Blood Lipoids, Arch. Int. Med., 1922, 30, 563. (An interesting low cholesterol in obesity has also been noted by Luden, personal communication: 0.13 gm. per 100 cc in a woman weighing 390 pounds.)
10. Bloor, W. R.: The Lipoids of the Blood, Jour. Biol. Chem., 1916, 26, 425 (Joslin's Case No. 786, Cl.).
11. Bloor, W. R.: Lipemia, Jour. Biol. Chem., 1921, 49, 201 (Case H.).
12. Bloor, W. R.: Lipemia, Jour. Biol. Chem., 1921, 49, 201 (Joslin's Case No. 786, Cl.).
13. Luden, G.: Observations on Cholesterin, Jour. Lab. and Clin. Med., 1916, 1, 669; 1917, 3, 141; 1918, 4, 849; 1919, 4, 719.
14. Benedict, S. R., and Lewis, R. C.: The Sugar Content of the Blood in Cancer, Med. Rec., 1914, 86, 650.
15. Huthle, K.: Ueber die Fettsäure-Cholesterin-Ester des Blutserums, Ztschr. f. physiol. Chem., 1895, 21, 349. Ellis, G. W., and Gardner, M. T.: The Origin and Destiny of Cholesterol in the Animal Organism, VIII and IX, Proc. Roy. Soc. London, Series B, 1912, 84, 466; 1912, 85, 385. Rothschild, M. A.: Zur Physiologie des Cholesterinstoffwechsels, V. der Cholesteringehalt des Blutes und einiger Organe in Hungerzustand, Beitr. z. path. Anat., 1915, 60, 227. (This paper shows most definitely the rise in the blood lipid content after fasting.) Gray: Loc. cit., reference No. 3. Bang, I.: Ueber Lipämie II, Biochem. Ztschr., 1918, 91, 105. Blau, N. F., and Nicholson, S. T.: Fat Metabolism in Diabetes Mellitus, Arch. Int. Med., 1920, 26, 743. Cowie, D. M., and Hoag, L. A.: Studies in Blood Fat, Jour. Am. Med. Assn., 1921, 77, 1493.
16. Marsh, P. L., and Waller, H. G.: Relation between Ingested Fat and the Lipemia of Diabetes Mellitus, Arch. Int. Med., 1923, 31, 63.
17. Personal communication.

SPLENECTOMY, ITS END-RESULTS AND CLINICAL INDICATIONS.

BY RALPH C. LARRABEE, M.D.,
VISITING PHYSICIAN TO THE BOSTON CITY HOSPITAL.

INTEREST in the subject of splenectomy has for more than a decade centered largely about the subject of pernicious anemia. Its benefits in that disease are still largely problematical and time has decreased rather than augmented the enthusiasm for it. Among physicians the discouraging results of splenectomy in pernicious anemia have brought about an undeserved distrust of splenectomy in general. This is unfortunate, for there surely are conditions in which the procedure is of the greatest value. With the object of showing what may be expected in properly chosen cases, the present brief series is reported.

Case Reports.—Rupture of Normal Spleen. CASE I.—E. C., male, aged thirty-four years. This previously healthy man was brought to the Boston City Hospital on November 28, 1908, immediately after having been injured in a railroad accident. Dr. F. J. Cotton removed the ruptured spleen. There was much blood in the abdomen. No transfusion was done either before or after operation.

About ten months later a lymph node could be felt in the left neck and later another in the groin. These gradually subsided and there was never anything resembling general glandular enlargement. Except for slight backache and vague pains in the upper abdomen in the first year or two after operation he has remained perfectly well.

Unfortunately this spleen was not examined microscopically, but there is no reason to suppose that it was diseased.

This is the only case of removal of a normal spleen in this series. The continuance of health after splenectomy is in agreement with the observations of many other writers. The blood changes differ from those found clinically and experimentally by certain workers, but comment on the matter will be deferred until later in this paper.

Five Cases of Splenic Anemia. CASE II.—R. C., female, aged thirty years, an Italian woman, who had for three years noticed a tumor low down in the left abdomen, slowly increasing in size. It was somewhat painful and there was an indefinite story of debility, dyspnea and nosebleed. She was operated upon by Dr. C. G. Cumston, March 29, 1904. The tumor proved to be a greatly ptosed spleen, weighing about 450 gm. (the normal is 150 to 250 gm.).

LARRABEE: SPLENECTOMY

CASE I.—SPLENECTOMY FOR TRAUMA, NOVEMBER 28, 1908.

Date.	Hemoglobin, per cent.	Red corpuscles.	White corpuscles.	Differential count in percentages.				
				Polymorphonuclear neutrophils.	Lymphocytes.	Large mononuclears and transitionals.	Eosinophiles.	Mast cells.
Dec. 15, 1908	89	4,048,000	8700	69.9	21.6	4.5	2.7	1.0
" 31, 1908	99	5,200,000	7800	64.7	22.6	7.1	4.2	1.2
Jan. 29, 1909	100	5,184,000	9300	48.4	37.1	6.9	6.0	1.4
Apr. 7, 1909	101	5,568,000	7200	37.0	47.3	9.8	3.4	1.2
June 14, 1909	105	5,352,000	5100	52.5	34.0	9.0	3.5	1.0
Oct. 4, 1909	110	4,936,000	4900	55.9	27.9	11.5	3.7	0.7
Jan. 11, 1910	112	5,204,000	7550	59.9	29.9	5.5	3.6	0.9
May 19, 1910	114	5,669,000	7400	53.7	34.5	7.8	2.7	1.0
Nov. 14, 1910	121	6,112,000	6300	56.8	30.4	7.6	3.2	2.0
Apr. 5, 1911	103	5,200,000	8000	59.0	26.0	12.0	1.0	2.0
Oct. 18, 1921	93	5,004,000	8200	62.6	23.4	8.4	5.8	0.8

Oct. 18, 1921: Platelets, 152,000; hemolysis in NaCl solution begins at 0.375 per cent and ends at 0.275 per cent.

No Howell-Jolly bodies, nucleated red cells or myelocytes were seen in any of the smears examined.

CASE II.—REMOVAL OF ENLARGED AND DISPLACED SPLEEN, MARCH 29, 1904.

Date.	Hemoglobin, per cent.	Red corpuscles.	White corpuscles.	Differential count in percentages.				
				Polymorphonuclear neutrophils.	Lymphocytes.	Large mononuclears and transitionals.	Eosinophiles.	Mast cells.
Mar. 30, 1904	75	5,680,000	13,800	82.6	6.2	9.0	2.0	0.2
Apr. 6, 1904	80	6,488,000	7,700	52.7	15.0	13.7	18.0	0.6
" 12, 1904	65.0	15.0	16.0	4.0	0.0
" 18, 1904	..	5,680,000	10,600	48.8	9.2	16.4	24.8	0.8
May 4, 1904	70	4,896,000	11,500	58.0	13.5	10.0	17.5	1.0
Aug. 5, 1904	80	4,900,000	14,400	65.0	11.7	11.7	11.0	0.6
Sept. 9, 1904	70	4,752,000	10,750	52.0	20.6	7.4	18.4	1.6
Nov. 30, 1904	90	5,208,000	7,400	40.4	25.9	13.4	19.5	0.8
Mar. 22, 1905	95	4,584,000	10,800	64.6	13.9	11.0	10.3	0.2
Nov. 24, 1905	85	4,636,000	13,200	64.8	19.7	7.6	7.6	0.3

No myelocytes or nucleated red corpuscles in any of the smears.

Five months after operation she had a sore throat, accompanied by slight, general enlargement of the lymph nodes, which subsided promptly. There was some complaint of pain in the upper abdomen

and back, and twice it was noted that the gums were red and somewhat swollen. Otherwise she remained in good health throughout the period of observation, twenty months.

Sections of the spleen have recently been examined by Dr. F. B. Mallory, who reports as follows: Capsule, thin; trabeculae, slender; arteries and lymph nodules, negative. Blood sinuses were very distinct and the walls were thickened, showing that stroma of the pulp is increased in amount. No eosinophiles found. Numerous polymorphonuclear and endothelial leukocytes in the blood sinuses. Diagnosis: Chronic splenitis.

CASE III.—E. B., male, aged fourteen years, came under observation in January, 1905. There was a history of pallor, fatigue, dyspnea and pain in the left side for at least three years. The liver was normal, the spleen 3 cm. below the costal margin. There were small lymph nodes in axillae and groins. The degree and type of anemia is shown in the table. During the three years that preceded operation his weakness and disability slowly increased. Both nodes and spleen became larger, the latter finally reaching 9 cm. below the ribs. Sexual development was retarded and at the age of seventeen years, the breasts were large; there was no axillary and little pubic hair, and erections had not occurred.

CASE III.—SPLENECTOMY FOR BANTI'S DISEASE, MARCH 25, 1908.

Date.	Hemoglobin, per cent.	Red corpuscles.	White corpuscles.	Differential count in percentages.				
				Polymorphonuclear neutrophils.	Lymphocytes.	Large mononuclears and transitionals.	Eosinophiles.	Mast cells.
Jan. 23, 1905 . . .	60	3,244,000	6,100	77.6	15.2	4.4	2.0	0.8
Mar. 16, 1905 . . .	70	4,152,000	6,200	63.8	20.2	7.2	7.4	1.4
July 3, 1905 . . .	65	3,080,000	5,900	69.4	21.0	6.3	3.3	3.0
Aug. 14, 1906 . . .	60	3,256,000	15,870	81.7	10.0	6.3	2.0	0.0
Aug. 19, 1907 . . .	50	2,704,000	10,700	71.4	18.7	5.0	4.2	0.7
Mar. 3, 1908 . . .	62	3,160,000	9,900	75.0	18.6	1.7	3.7	1.0
" 15, 1908 . . .	76	3,516,000						
" 26, 1908 . . .	88	3,798,000	38,000	88.6	3.1	8.1	0.0	0.0
" 30, 1908 . . .	89	4,416,000	15,700	69.6	21.5	6.2	2.7	0.0
Apr. 10, 1908 . . .	93	4,800,000	27,400	63.8	25.9	6.0	2.8	1.5
" 30, 1908 . . .	104	5,080,000	11,600	66.5	18.6	7.6	6.3	1.0
July 28, 1908 . . .	99	5,008,000	16,600	53.2	25.2	5.7	14.7	1.2
Aug. 11, 1908 . . .	100	17,000					

Splenectomy was done, March 25, 1908, by Dr. Hugh Cabot. After a somewhat stormy convalescence he showed most marked and

gratifying improvement. His color improved, and, in two weeks the anemia, which had resisted treatment by iron, arsenic and other medical means for three years, had disappeared. He remained well until August 10, 1908, four and a half months after operation when he died of acute appendicitis.

Autopsy by Dr. Mallory showed general peritonitis and bronchopneumonia. The mesenteric lymph nodes were enlarged and firm, Peyer's patches slightly reddened. The bone-marrow was red. The liver weighed 1425 gm.; microscopically it was normal. Spleen (removed at operation, four and a half months before death), capsule thin, trabeculae slender and not numerous; arteries and lymph nodules negative. Blood sinuses distinctly outlined. Stroma between them moderately increased in amount. Eosinophiles fairly numerous in pulp. Diagnosis: Chronic splenitis.

CASE IV.—C. K., female, aged thirty-eight years, was seen in consultation with Drs. W. Y. Fox and A. R. Crandell, of Taunton. Her illness began abruptly with severe hemorrhage from the stomach in April, 1917. Milder hemoptysis occurred a month later, and again about January 1, 1918. Ascites was first noticed, after parturition, in September 1917, and enlargement of the spleen in February, 1918, after tapping. When seen a week later, the abdomen had partly refilled with fluid, but the spleen could still be felt. It filled the left half of the abdomen down to the crest of the ilium. The liver was not palpable.

On March 2, 1918, she was transfused and the spleen immediately removed by Dr. Edward Richardson. The liver was felt to be considerably enlarged and finely irregular. Improvement was prompt and striking, and at the end of a month she resumed her household duties. On April 27, however, she became suddenly ill, with temperature of 104° F. One of her children had scarlet fever, but the patient presented no evidence of this disease. Chills, sweats and fever of a septic type continued and she died in August, above five months after operation. The cause was assumed to be septic endocarditis, although definite demonstration of this condition was lacking.

The blood, eleven days before splenectomy was as follows: Hemoglobin, 43 per cent; red corpuscles, 2,840,000; leukocytes 750; polymorphonuclear neutrophiles, 66 per cent; lymphocytes, 18 per cent; endothelial leukocytes, 16 per cent. Smears showed only slight changes in color, size and shape of the red corpuscles; no erythroblasts; the platelets seemed much decreased.

On July 9, about four months after operation, and ten weeks after the onset of the septic fever the figures were as follows: Hemoglobin, 66 per cent; red corpuscles, 2,552,000; leukocytes, 19,000; polymorphonuclear neutrophiles, 88.5 per cent; lymphocytes, 6.5 per cent; mast cells, 1.5 per cent; platelets about normal.

The spleen was examined by Dr. W. F. Whitney: "It was smooth externally and measured 23 by 15 by 5 cm. On section it was homogeneous, the follicles were indistinct, and of firm consistency. Microscopical examination showed proliferation of the endothelial lining of the blood sinuses, in places forming a low grade of connective tissue. Diagnosis: Chronic hypertrophy."

CASE V.—M. J., female, aged forty years. She admitted taking an occasional glass of ale. She had malaria in 1909 and an abdominal operation in 1912, at which time she was told that her spleen was enlarged. After this she had occasional "spells," lasting a few days and characterized by swelling of the abdomen. In August, 1919, she began to lose weight, and to suffer from dyspnea and steadily increasing distension. She came to the City Hospital, October 11, 1919. There was moderate emaciation and pallor, marked ascites, and a spleen which extended slightly below the navel. The liver was not palpable. The hemoglobin was 20 per cent; red corpuscles, 1,664,000; leukocytes, 1490; polymorphonuclear neutrophils, 85 per cent; lymphocytes, 8 per cent, large mononuclears, 7 per cent; no nucleated red corpuscles; moderate achromia; platelets probably somewhat decreased.

The abdomen was tapped twice, a total of 15½ quarts of clear fluid being removed. On October 30, Dr. A. R. Kimpton transfused 900 cc of blood. This was followed by a rise of hemoglobin to 45 per cent and by much clinical improvement. Splenectomy was done, November 4, by Dr. Kimpton. At operation a hard, hobnailed liver was felt. She left the table in severe shock and died the next morning. This is the only operative death in the series.

The spleen weighed 7000 gm. Microscopically it showed congestion and fibrosis as in the others of this group.

CASE VI.—M. W., female, aged fifty-six years. Patient of Dr. E. T. Manix, of Lynn. There was nothing in the history or physical state to suggest alcoholism or syphilis. She gave a history of "indigestion" for thirty-nine years, with repeated hematemesis. When seen by the writer in September, 1919, pallor, weakness and dyspnea had been progressive for seven years. She was moderately emaciated and pale. The liver edge could be felt only on deep inspiration. The spleen extended 4 cm. below the costal margin. By January, 1920, the spleen had increased to 10 cm., the liver was no longer palpable, and there was slight ascites. Roentgen-ray showed gall stones and an hour-glass stomach, with what appeared to be an active ulcer. The Wassermann test was negative.

Two transfusions resulted in much improvement. Splenectomy was done, February 10, 1920, by Dr. A. R. Kimpton. There was some ascites and the presence of gall stones and an hour-glass stomach was verified, though neither of these lesions was operated upon.

LARRABEE: SPLENECTOMY

CASE VI.—SPLENECTOMY FOR BANTI'S DISEASE, FEBRUARY 10, 1920.

Date.	Hemoglobin, per cent.	Red corpuscles.	White corpuscles.	Differential count in percentages.						Nucleated red corpus- cles.	Reticulo- cytes per cent	Platelets.	Remarks.
				Polymorphonuclear neutrophils.	Lymphocytes.	Large mononuclears and transitionals.	Eosinophiles.	Mast cells.	Myelocytes.				
Sept. 5, 1919	33	2,136,000	1,650	67.0	28.0	2.0	2.0	2.0	1.0	0	7.5	Decreased	Transfused Jan. 23. Transfused Feb. 2.
Jan. 14, 1920	24	1,800,000	3,600	72.0	16.0	4.0	3.0	0	0.0	0	0.6	Decreased	
Jan. 27, 1920	41	3,300,000	2,800	60.0	32.0	4.0	4.0	0	0.0	0	2.4	Decreased	
Feb. 4, 1920	51	3,800,000	6,000	52.5	35.0	12.5	0.0	0	0.0	0	...	Increased	
" 11, 1920	52	4,000,000	8,000	82.5	14.0	2.0	0.5	0	1.0	Many Few	3.6		
" 12, 1920	52	4,000,000	8,000	87.5	3.5	1.5	1.0	0	7.5		3.8		
" 14, 1920	52	3,500,000	10,200	79.0	4.0	5.0	1.5	1	9.0		5.2		
" 20, 1920	56	3,800,000	6,600	77.5	5.0	2.0	1.5	0	13.0		3.4		
Mar. 2, 1920	60	4,000,000	7,000	40.0	40.0	12.0	0.0	8	...		5.7		
Mar. 9, 1920	62	4,300,000	7,000	40.0	39.0	10.0	8.0	1		
Apr. 3, 1920	50	2,300,000	5,000	55.0	24.0	15.0	1.0	2	0.5		...	600,000	Hemorrhoids, bleeding.
May. 4, 1920	76	3,750,000	5,600	50.0	34.5	13.0	0.5	2	...	0	1.1	Abundant	
Nov. 10, 1920	88	3,360,000	5,400	41.0	46.0	11.0	0.0	1	1.0		0.9	596,000	
Apr. 10, 1923	73	3,184,000	8,850	50.5	33.0	12.5	2.0	1	1.0	0	...	248,000	Recent hemorrhage.

The clinical results were excellent. The anemia improved, but did not wholly clear up—which is not remarkable when it is remembered that an active gastric ulcer was left undisturbed and that she continued to bleed from hemorrhoids. The need for further operative work was recognized, but she refused, perhaps wisely, to see the matter in this light.

The spleen weighed 510 gm. Dr. Mallory reported: "Congestion and fibrosis; no thrombosis of portal or splenic vein."

Recently (April, 1923), she has had for the first time since operation a slight hemorrhage from the stomach. After a couple of days in bed, she got up and went about her daily housework as usual. She now considers herself perfectly well, as there is nothing the matter with her except cirrhosis of the liver, gall stones, gastric ulcer, hemorrhoids and a considerable degree of vascular hypertension.

Cases II to VI obviously belong in the clinical group characterized by a large fibrotic spleen, the secondary type of anemia with leukopenia, tendency to hemorrhage from the stomach and ascites in the later stages, and susceptibility to marked improvement after splenectomy. Of course they do not all show all of these symptoms, Case II in particular representing an early stage. Most clinicians will classify such cases either as splenic anemia or as Banti's disease, although in the present state of knowledge it is safer to classify them by definition rather than by name. Writers have differed in their use of the term "Banti's disease," especially as regards the significance of the changes in the splenic and portal veins. Apparently Banti himself, in his long series of papers expressed different views at different times. As regards what to include under the term splenic anemia, the writer is in accord with the characteristically vigorous words of W. J. Mayo,³ who says that, inasmuch as cases are taken out of this category as soon as the etiology is known, "incomplete knowledge is essential to the diagnosis. . . . I believe we would get a better idea of splenic anemia if we made the pathological condition of the spleen and its effect on the blood the criterion, and classified as splenic anemia all cases of known causation as well as those of unknown causation."

The most significant question here concerns the relationship of such cases as these with cirrhosis of the liver. That such association does exist, at least in the later stages, is of course well known. Banti and most of the earlier writers on this subject considered the changes in the liver to be secondary to those in the spleen.^{1 4} Of late the question as to whether the changes in the liver or vessels may not be the primary factor is becoming more insistent.

The spleens of the cases herewith reported show nothing that could not be explained by long continued chronic passive congestion. Dr. F. B. Mallory, who examined most of them, states that the changes are precisely those that occur in ordinary cases of alcoholic cirrhosis. Not one of these patients gave a history of alcoholism

and surely four women and one young boy hardly constitute a group in which one would expect chronic alcoholism to be the common etiological factor. Yet at operation three showed livers which seemed cirrhotic. One had a spleen so greatly ptosed that its position might have been the cause of chronic congestion. The remaining case showed a normal liver at autopsy. As he lived several months after splenectomy, the condition of the splenic vessels can not be stated. It should be said that chronic passive congestion of the spleen does not necessarily imply cirrhosis of the liver though that is perhaps the commonest cause—sclerosis or thrombosis of the splenic or portal vein above the junction, or marked ptosis of the spleen, would give the same conditions—at least in a mechanical sense.

Whatever may be the solution of this problem, the important clinical fact is that these big, fibrotic spleens, however brought about, are, at least potentially, causes of anemia and after their removal the anemia promptly clears up. Further, the ascites and hemorrhages occurring in the later stages may be greatly improved and often made to disappear by the same operation. It will greatly clear the air if clinicians will bear these facts in mind, and not be too fussy about the primary cause of the splenomegaly.

Two Cases of Alcoholic Cirrhosis. CASE VII.—J. F., male, aged twenty-five years, was referred to me by Dr. H. P. Towle. This man was a steady drinker, who had, when he came under observation, suffered for but two weeks from dyspnea, edema and ascites. He was pale and delicate-looking, with the velvety skin characteristic of the confirmed alcoholic. He had mild psoriasis. The abdomen was greatly distended with fluid and there was much hard, brawny edema of the legs. The liver could not be felt. The spleen was 5 cm. below the ribs. The urine contained [a slightest possible trace of albumin, but no casts.

After being tapped twice at intervals of a week, splenectomy was performed by Dr. H. B. Loder. At operation the liver was felt to be hard and "hobnailed." He was followed for ten weeks after operation, during which period there was little if any ascites and no edema. Perhaps, because he felt the need of a less arid climate, he then went to Ireland, where he became involved in the prevailing political disorders and was repeatedly arrested. He returned to Boston and reported for examination twenty-one months after the splenectomy, feeling perfectly well and still free from edema and ascites. The urine contained a large trace of albumin, hyaline and granular casts and blood cells. These soon disappeared under treatment, but when last seen, he had slight glycosuria. The psoriasis cleared up shortly after operation and recurred for only one short period nearly two years later.

The spleen weighed 690 gm. Dr. Mallory reported: "Marked fibrosis and moderate congestion."

CASE VII.—SPLENECTOMY FOR CIRRHOSIS OF THE LIVER, JUNE 18, 1920.

Date.	Hemoglobin, per cent.	Red corpuscles.	White corpuscles.	Differential count in percentages.						Normo- blasts.	Megal- blasts.	Reticulo- cytes, per cent.	Miscellaneous.
				Polymorphonuclear	Lymphocytes.	Large mononuclears	Eosinophiles.	Mast cells.	Myelocytes.				
May 26, 1920	100	4,000,000	2,800	64.5	25.5	7.5	1.5	1.0	0.0	0	0	1.6	Congulation factors normal.
June 18, 1920	95	4,500,000	2,200	66.0	18.5	5.0	10.0	0.5	0.0	0	0	2.1	Before splenectomy.
" 18, 1920	92	4,800,000	5,000	59.0	28.0	3.0	10.0	0.0	0.0	2	4	...	After splenectomy.
" 19, 1920	92	4,800,000	14,000	51.0	6.5	9.0	0.0	0.0	3.5	0	0	3.0	Platelets diminished.
" 21, 1920	62	3,800,000	17,000	82.5	9.5	7.5	0.5	0.0	0.0	0	0	6.2	Platelets increased.
" 26, 1920	80	3,870,000	20,800	85.0	2.5	9.5	1.5	0.0	1.5	0	0	...	Platelets, 800,000.
" 30, 1920	97	4,100,000	20,200	82.5	5.5	3.5	1.0	0.0	7.5	0	0	6.8	Platelets, 278,000.
July 6, 1920	102	4,200,000	7,600	77.5	11.0	1.0	1.5	1.5	7.5	0	0	9.5	Platelets normal.
" 13, 1920	127	4,900,000	20,400	74.5	9.0	9.5	2.5	0.0	4.5	0	0	2.8	...
Aug. 6, 1920	74	3,930,000	8,500	48.0	36.0	6.0	4.0	2.0	4.0	0	0	1.3	...
Apr. 1, 1922	84	4,056,000	11,000	64.0	20.5	12.5	2.0	1.0	0.0	0	0	...	Platelets, 152,000.

CASE VIII.—D. B., aged fifty years, an Italian laborer, who used wine freely. He came to the Boston City Hospital for hernia. During the routine examination, the liver and spleen were both found to extend 5 cm. below the costal margin. There was slight jaundice, but no ascites. The Wassermann reaction was negative. He refused operation for the hernia and was discharged. About three months later he was readmitted with marked ascites, jaundice and edema of the legs.

Splenectomy was done by Dr. J. C. Hubbard. At operation both spleen and liver were adherent to adjacent structures. The liver was not noticeably enlarged; adhesions prevented satisfactory palpation.

The results were disappointing as compared with the preceding case. There was some improvement in his general condition and the anemia disappeared, but he continued to need tapping about once a month. He was lost sight of after four months.

The spleen was the size of two fists. Dr. Mallory's report was, "Increase of stroma; chronic fibrosis."

CASE VIII.—SPLENECTOMY FOR CIRRHOSIS OF LIVER AND SPLENO-MEGALY, AUGUST 18, 1921.

Date.	Hemoglobin, per cent.	Red corpuscles.	Leukocytes.	Differential count in percentages.					Platelets.
				Polymorphonuclear neutrophils.	Lymphocytes.	Large mononuclears and transitionals.	Eosinophiles.	Mast cells.	
Aug. 1, 1921	70	3,180,000	4,000	70.0	29.0	1	0	0	Decreased. 166,000
" 22, 1921	75	2,280,000	14,000	91.0	6.0	3	0	0	
Oct. 5, 1921	96	4,500,000	12,600	53.5	27.5	18	1	0	

These two cases are classed as cirrhosis of the liver chiefly because they were alcoholics. So far as the structural changes in the spleens are concerned, they might equally well have been classed in the preceding group, and Case VIII, as he had the characteristic anemia which cleared up after splenectomy, should perhaps have been so classed. The truth is that cirrhotic splenomegaly and splenomegalic cirrhosis are so closely allied that a distinction is impossible, clinically or pathologically, and it seems quite pointless to make the existence of changes in the splenic or portal vein the criterion.

Mayo⁶ has reported 11 splenectomies for portal cirrhosis, with 4 deaths—not a very high mortality when it is considered that all 11 were advanced cases with ascites and hemorrhages from the

stomach. Any internist who has handled such cases knows how hopeless they are under medical treatment. Four of Mayo's cases were greatly benefited, 1 being alive five years after operation.

The beneficial effects of splenectomy in cirrhosis have been attributed partly to cutting off the supply of toxic material presumably elaborated in the spleen and passed on to the liver, and partly to mechanical relief of the portal circulation. The existence of any such toxic material is wholly hypothetical, but there can be no doubt of the mechanical relief. The blood supply of the spleen is very large and it is said that normally 25 to 30 per cent of the portal blood comes from the splenic vein. Presumably in these enormously enlarged spleens the proportion is much higher. The relief to the narrowed portal channels from the cutting off of this large amount of blood is probably enough to account for the effect of the operation on ascites and hemorrhages. Splenectomy alone was done in both cases here reported. Mayo combines splenectomy with omentopexy.

Hemolytic Jaundice. CASE IX.—J. S., male, aged twenty-seven years. His illness began in the fall of 1919 with acute pain in the left side followed by jaundice, which, he thought, had not cleared up. He complained only of drowsiness and debility. When seen, March 26, 1920, there was but slight pallor, the complexion being a muddy yellow—he was not definitely jaundiced. The liver was slightly enlarged and the hard edge of the spleen was felt at the level of the umbilicus. There was no history of alcoholism, and the Wassermann reaction was negative. The blood findings including fragility tests and reticulated red counts are shown in the chart.

Splenectomy was done by Dr. F. J. Cotton on May 28, 1920. There were no adhesions, no ascites and no definite enlargement of the liver. The patient, who had, it is true, not been very ill or wholly incapacitated, expressed himself as being greatly improved. When last seen (September, 1921) his condition remained normal.

The spleen weighed 865 gm. Dr. Mallory reported only congestion and fibrosis.

This is obviously the acquired (Hayem-Widal) type of hemolytic jaundice, the distinguishing features being the marked fragility of the red corpuscles, and the large percentage of reticulated red corpuscles previous to the disappearance of the anemia after operation. The acquired type, unsplenectomized, is universally admitted to be less favorable in prognosis than the congenital, and therefore to a greater extent an indication for splenectomy. This patient was told that he might live for years without splenectomy, but that operation, if successful, would relieve his symptoms. He elected to take the risk. It seems to the writer that the question should always be put up to the patient in some such way. This subject has been thoroughly covered in the recent monograph of Tileston,⁶ and further comment seems unnecessary.

CASE IX.—SPLENECTOMY FOR HEMOLYTIC JAUNDICE, MAY 28, 1920.

Date.	Hemo- globin, per cent.	Red corpuscles.	Leuko- cytes.	Differential count in percentages.						Normo- blasts.	Hemolysis in hypotonic NaCl solution in percentages.		Reticulo- cytes, per cent.	Miscellaneous.
				Polymorphonuclear neutrophils.	Lymphocytes.	Large mononuclears and transitionals.	Eosinophiles.	Mast cells.	Myelocytes.		Begins.	Ends.		
Apr. 1, 1920	61	3,500,000	8,200	80.0	14.0	4.0	1.0	1.0	0.0	0	0.575	0.450	16.0	Coagulation factors normal; serum urobilin +. Platelets, 300,000. Blood from splenic artery. Blood from splenic vein.
May 14, 1920	89	3,200,000	5,000	53.5	32.0	13.5	0.5	0.0	0.5	0	.600	.400	11.7	
" 28, 1920	65	9,400	9,400	39.2	58.4	1.7	0.4	0.0	0.0	0	0.600	0.400	14.5	
" 28, 1920	75	3,500,000	18,800	30.5	58.0	11.0	1.5	0.0	0.0	0	0.600	0.425	7.2	
" 29, 1920	72	5,500,000	17,200	91.0	6.0	3.0	0.0	0.0	0.0	0	13.4	
June 2, 1920	95	5,700,000	5,200	48.0	33.0	16.0	3.5	0.5	0.0	0	.550	.450	3.8	Platelets appear increased.
" 4, 1920	95	4,900,000	8,400	57.5	26.5	9.5	2.0	0.0	4.5	1	0.500	0.350	2.1	Platelets appear decreased.
" 15, 1920	89	5,300,000	6,000	34.8	45.6	11.3	3.5	1.0	3.5	1	0.500	0.300	1.0	Platelets appear increased.
" 30, 1920	117	5,400,000	10,400	42.5	44.5	11.5	3.0	0.0	1.5	0	0.500	0.300	2.3	Platelets appear increased.
Aug. 12, 1920	110	5,430,000	8,700	32.5	53.0	8.5	3.0	2.0	0.0	0	0.475	0.350	0.6	Platelets appear increased.
Sept. 24, 1920	111	6,880,000	19,400	Platelets, 438,000.
Sept. 9, 1921	70	6,400,000	12,000	Smears normal.

Hypoplastic Anemia. CASE X.—O. S., male, aged thirty years. This was an unusual case of "chronic aplastic anemia," or "hypoplastic anemia," which will be reported in detail later. The condition is known to have existed since 1915, for an examination of the blood by Dr. A. A. Hornor at that time showed anemia of the peculiar type so evident later. He had several attacks of jaundice and hemorrhages into the skin, from the nose, from tooth extraction and particularly into the vitreous of the right eye, the latter having recurred frequently for six years.

He was referred to the writer by Dr. E. W. Clap in February, 1920. He was pale, with a peculiar yellowish, "sour-dough" tinge. The vitreous of the right eye was opaque and there was a retinal hemorrhage on the left. On the shins there were purpuric spots and some old, brown, pigmented areas. Neither liver, spleen nor lymph nodes were palpable. No relief resulted from any of the various therapeutic measures tried, except from transfusion. In all he received eighteen transfusions, aggregating about 10,000 cc of blood. Each caused general improvement and temporary cessation of hemorrhage, but after a few days or weeks the anemia and the bleeding would recur with increasing intensity till he was again transfused.

Splenectomy was undertaken as a last resort in the hope of bringing about increased resistance of the red cells as well as increased activity of the marrow. After four preliminary transfusions, Dr. Kimpton removed the spleen on July 1, 1921. There was no bleeding and convalescence was uneventful.

The results, so far as retarding the advance of the anemia is concerned, were disappointing. Inspection of the accompanying table will show, however, that the figures for platelets ran distinctly higher than before, and it is notable that there were no further hemorrhages—about the only practical benefit which the patient derived from the operation. He died in February, 1922. There was no autopsy.

The spleen was slate gray, measured 11 x 8 x 5 cm., was of rather firm, rubber-like consistency, and the cut section was dark red. Microscopically it showed chronic splenitis.

Hodgkin's Disease. CASE XI.—N. W., female, aged sixty-five years, was referred by her family physician to Dr. J. L. Ames, through whose kindness I saw her after operation and am permitted to include her case in this series. In December, 1920, she had some minor digestive symptoms and rapidly lost strength and color. A month later the enlarged spleen was noticed. It increased rapidly until it extended inward to the median line and downward below the umbilicus. There was a tumor, apparently an enlarged lymph node, about the size of a walnut, under the angle of the jaw on the right, and some smaller nodes in the neck. There was no jaundice

and no ascites. Her general condition was very unfavorable and she seemed unlikely to live more than a few weeks.

Splenectomy was successfully done by Dr. F. G. Balch, January 14, 1921. The gland in the neck was afterward treated by the Roentgen-ray without effect and is still about its original size. Now, over two years after operation, the patient considers herself perfectly well.

The blood, just before operation was as follows: Hemoglobin, 60 per cent; red corpuscles, 2,700,000; leukocytes, 5000; platelets, as seen in smears, apparently decreased. On February 3, 1921, three weeks after the operation, the blood was examined by the writer with the following results: Hemoglobin, 56 per cent; red corpuscles, 2,760,000; leukocytes, 16,000; platelets, 380,000; volume index,⁷ 1.27; polymorphonuclear neutrophils, 93.5 per cent; lymphocytes, 3.5 per cent; large mononuclears and transitionals, 1.5 per cent; mast cells, 0.5 per cent; myelocytes, 1 per cent; rare normoblasts; reticulocytes 1.5 per cent. On April 20, 1923: Hemoglobin, 87 per cent; red corpuscles, 4,616,000; leukocytes, 7400; platelets, 336,000; polymorphonuclear neutrophils, 63 per cent; lymphocytes, 30 per cent; large mononuclears and transitionals, 5 per cent; eosinophiles, 2 per cent; reticulocytes, 0.2 per cent.

The spleen was about 10 inches long. It presented a number of opaque nodules which proved to be infarcts. Microscopically it showed large, confluent masses of lymphoblastic tissue, with mitotic figures. Dr. J. Homer Wright's diagnosis was Hodgkin's disease.

This case is probably to be classed as Hodgkin's disease, that is, lymphoblastoma without massive invasion of the blood by newly formed lymphocytes. However, in the absence of the usual clinical feature of widespread involvement of lymph nodes, and particularly in view of the widely different views of pathologists as to what constitutes this disease, it is perhaps best not to be certain. The usual method of handling such a case would doubtless be to begin by excising the gland in the neck for histological examination. Had this been done and had the examining pathologist reported Hodgkin's disease or lymphoblastoma, it is improbable that splenectomy would have been performed. This patient refused to have the gland removed, as a previous attempt to do so had resulted in a bothersome hemorrhage. This and the favorable outcome disarms criticism, and even if relapse should occur now, over two years after operation, the procedure has justified itself. It is possible that this case was one of the rare instances of primary Hodgkin's disease of the spleen, and that the hypertrophy of the cervical glands was an independent lesion. If cases of Hodgkin's disease confined solely to the spleen occur, it would probably be impossible to differentiate them from splenic anemia until the spleen is removed and

examined. The case here reported justifies splenectomy in such conditions.

GENERAL COMMENT. *The Blood.* No comment is necessary on the blood conditions previous to operation, since these cases showed nothing different from the findings well known to exist in the diseases concerned. In certain ways, however, the effects of splenectomy on the blood pictures differed from the generally accepted facts.

After experimental splenectomy in normal dogs, Pearce, Krumbhaar and Frazier¹ observed secondary anemia which increased for about six weeks, and gradually disappeared in three months or more. Wolferth⁸ found similar changes in rats and Hitzroth² the same in 4 human cases splenectomized for trauma, as well as in several patients where diseased spleens were removed.

Unfortunately there was no examination of the blood in the only normal spleen in my series until the seventeenth day, at which time the figures showed evidence of an unusually rapid recovery from the severe loss of blood from the ruptured organ. By the end of a month there was slight polycythemia, which persisted for at least two years. Only one of the splenectomies for disease (Case VII) was followed by definite increase of anemia, and in this case it lasted but twelve days. Of the five previously anemic cases in which adequate studies of the blood were made both before and after operation, only one, the hypoplastic anemia (Case X), failed to show prompt improvement in the anemia. One (III) was normal in two to four weeks, one (VIII) in six weeks, and one (IX) in five days. In the remaining case (VI) the effects of splenectomy were masked by the facts that several transfusions had been done previous to splenectomy and that her hemorrhoids continued to bleed for several weeks afterward, but the beneficial effects were shown by the persistence of the artificially high figures existing as a result of transfusion before operation and by the gradual establishment of a normal blood in the months following.

On the whole the improvement as regards the anemia was more striking than these figures would indicate. In cases IV and XI, both seen in consultation, improvement was so obvious that the physicians in charge considered further study of the blood superfluous—which is gratifying enough, but not improving to the statistics!

The resistance of the red corpuscles to hemolysis in hypotonic salt solutions showed an increase after splenectomy in the few cases where it was studied—which is in accordance with the results of others. The case of hemolytic jaundice (IX), where resistance was low before operation, showed some increase after splenectomy, but the figures did not reach normal. It is interesting to note that in the normal case (I) the resistance remained abnormally high at the end of thirteen years.

Most of these cases showed a few nucleated red cells, usually

normoblasts, shortly after splenectomy. Only rarely were Howell-Jolly bodies seen. No case had any definite "blood-crisis." Neither was there any consistent effect on the proportion of reticulocytes.

In accord with the results of others, all of our cases (except the one with hypoplasia) showed leukocytosis after splenectomy. The degree of leukocytosis and the time the maximum figure was reached were so variable as to defy analysis, but in all but two or three the maximum was definitely above normal. In all but three the leukocytosis persisted as long as the cases were observed.

Analysis of the cell-types concerned in these leukocytoses is necessarily rather vague, since in normal individuals the different types undergo wide fluctuations and definite standards do not exist. In the first few days after operation the increase seemed due to polymorphonuclear neutrophils. Later, in the persistent stages, the lymphocytes and endothelial leukocytes (large mononuclears and transitionals) were also increased. Eosinophilia was present to a slight degree in most of the cases at variable periods after operation. Only in Case II was it marked and persistent—the highest figure being 25 per cent (2628 per c.mm.). It is often more apparent if absolute figures are used rather than percentages.

The platelets showed a decided tendency to increase in number after splenectomy. This is in accordance with the recent work of Brill and Rosenthal,¹⁰ who have advocated splenectomy for the relief of the thrombopenia of purpura hemorrhagica. While the figures are too incomplete to allow inferences as to the duration of this change, it may safely be said that it outlasted the period of recovery from operation and is therefore to be classed along with the increase of red corpuscles and leukocytes as a result of splenectomy *per se*. Case X is particularly interesting in this respect. Apparently his marrow was so damaged that it was unable to respond to splenectomy either by increased formation of red cells, or leukocytosis, but the platelet-forming function was still able to respond, though not in a normal degree.

Why does removal of the spleen lead to such prompt recovery from anemia? The answer might conceivably be that the abnormally active processes of blood destruction consequent upon the splenic disease are brought to a standstill by its removal. That splenectomy does, in fact, result in decreased elimination of pigment derived from hemoglobin may be accepted, and probably the beneficial effects of the operation are partly due to lessened blood destruction.

On the other hand the appearance in the blood of nucleated red corpuscles, the increase of leukocytes, including those types originating in the marrow, and of the platelets as well, would seem to indicate a speeding up of the process of blood-formation. Hyperplastic changes in the marrow after splenectomy have been

shown by various investigators.¹ It may be taken as a fact, then, that, while there is increased resistance to hemolysis of the red cells and decreased cell-destruction, there is also a marked increase in the activity of the blood-forming tissues consequent upon the loss of the spleen.

Fatalities. Four of the 11 cases here reported are known to be dead. One was an operative death and calls for no comment. Another was the case of hypoplastic anemia, in which splenectomy if it did not materially retard the downward course of the disease, certainly did not hasten it. Of the two remaining fatal cases, both splenic anemias, one (III) died four and a half months after operation, of acute appendicitis, the other (IV) in five months of an infection of unknown cause. Although these conditions would hardly seem to have any etiological connection with splenectomy, the cases are interesting in view of a considerable amount of experimental investigation on the influence of splenectomy on resistance to infection. Morris and Bullock⁹ summarized the literature in 1919. Their own extensive and carefully controlled work leaves no doubt that splenectomy greatly increases the susceptibility of rats to rat plague. The writer knows of no published evidence that similar increased susceptibility occurs in man. However, it would certainly seem wise to bear in mind the possibility of its occurrence, when considering the advisability of operation.

THE INDICATIONS FOR SPLENECTOMY. Splenectomy is indicated in most cases of clinical splenic anemia, without much regard to what causes the splenic enlargement. As many of the unoperated cases get along in comfort for years, it is reasonably safe to postpone operation until the anemia becomes incapacitating. Even after ascites and gastric hemorrhages have begun, operation will often result in clinical cure. In hemolytic jaundice it is generally indicated in the acquired and sometimes in the congenital cases and promises complete relief.

In alcoholic and other cirrhoses of the liver, it is indicated only in selected cases—mostly those in advanced stages with ascites. As the effects of splenectomy are probably for the most part purely mechanical, best results will be obtained where the spleen is unusually large and relief to the portal circulation is correspondingly great. If such patients also have anemia and leukopenia, they are clinically indistinguishable from, if not pathologically identical with, Banti's disease and splenectomy is by all means indicated.

Of several forms of splenic anemia not illustrated in my series, it may be said that in Gaucher's disease, splenectomy should generally be done, and that in von Jaksch's disease it is sometimes necessary. Evidence is accumulating to show that the enlarged spleens sometimes seen in syphilis, malaria and other chronic infections are not *per se* innocuous and their removal has in certain reported cases been followed by marked improvement.^{3 5}

It is generally admitted that splenectomy is contraindicated in leukemia, with which conclusion the writer emphatically agrees. Few cases have survived the operation, and even where skilled surgery has procured a successful operative result, there has been little or no gain to the patient.

Primary polycythemia is another condition frequently associated with splenomegaly in which splenectomy is contraindicated,¹ both on theoretical and clinical grounds. The question of splenectomy in pernicious anemia is still perhaps a moot point. It may be safely said that, while the operation has a place in the treatment of this disease, its value is limited, and the results obtained are in no way comparable with those seen in such diseases as splenic anemia and hemolytic jaundice.

One final caution: Splenectomy ought never to be decided upon hastily and without careful study of the case. A delay of several months is generally advisable. Otherwise, one may find out too late that he has mistaken leukemia in an aleukemic stage for Banti's disease, or polycythemia for hemolytic jaundice. Even if the patient is quite sick and in a stage of advanced anemia, a transfusion or two and a few abdominal taps will tide him along and perhaps, as in Case VI, lead to a degree of temporary improvement that will greatly increase the chance of success, besides giving opportunity for study. Reasonable delay will rarely injure the patient's chances and time is a great diagnostician.

NOTE.—Since this paper was presented for publication we have had three more splenectomies. The first was a case of chronic purpura hemorrhagica, in which complete relief has now lasted four months. The second was a case of pernicious anemia, the result of operation being a prolonged remission, but accompanied by little subjective improvement. The third was a remarkable case of anemia following pregnancy, which promptly recovered after splenectomy, repeated transfusions having failed.

REFERENCES.

1. Pearce, Krumbhaar and Frazier: *The Spleen and Anemia*, Lippincott, Philadelphia, 1918.
2. Hitzrot: *Ann. Surg.*, 1918, **67**, 540.
3. Mayo, W. J.: *Trans. Am. Surg. Assn.*, 1919, **37**, 483.
4. Moynihan: *The Spleen and Some of its Diseases*, 1921.
5. Mayo, W. J.: *Jour. Am. Med. Assn.*, 1921, **77**, 34.
6. Tileston: *Medicine*, 1922, **1**, 355.
7. Larrabee, R. C.: *Jour. Med. Res.*, 1911, **24**, 15.
8. Wolferth: *Arch. Int. Med.*, 1917, **19**, 105.
9. Morris and Bullock: *Ann. Surg.*, 1919, **70**, 513.
10. Brill and Rosenthal: *AMER. JOUR. MED. SCI.*, 1923, **166**, 503.

STUDIES IN CHOLELITHIASIS.

IV. THE LATE AND PERMANENT RESULTS OF THE VARIOUS TYPES OF OPERATION ON THE BILIARY PASSAGES WITH ESPECIAL REFERENCE TO THE CHOLESTEROL METABOLISM.

BY ABRAHAM O. WILENSKY, M.D.,

AND

MARCUS A. ROTHSCHILD, M.D.,

NEW YORK.

(From the Mount Sinai Hospital, New York City.)

IN previous studies¹ on cholelithiasis it was shown that knowledge of the actual anatomical conditions was necessary for a proper conception of the underlying pathological disturbance initiating disease of the bile passages with stone formation. Then it was possible to distinguish that the cases fell into a number of groups in one of which (1) the dominant factor was a disturbance of the cholesterol metabolism. (The other groups included (2) the purely infectious cases and (3) that in which infection and disturbed metabolism were intimately bound together.)

An investigation of the effect that the various types of operation² upon the biliary passages had upon these conditions, especially the effect upon the underlying metabolic disturbance when the latter was present, showed that in a certain number of the patients the immediate effect of the operation differed from the one ultimately to be observed if the cases were followed over long periods of time. These immediate effects can be summarized as follows:

A. The operation of cholecystectomy accomplishes two objects: (1) It removes the local focus of infection, when that is present; (2) it removes the reservoir of bile with its contained stones and stagnant bile, thereby also removing some of the end results of the pathological disturbance in the cholesterol metabolism which has already taken place: The former removes an agent which has complicated this biological disturbance or which has initiated the stone formation. The only permanent effect accomplished is the removal of the infectious process whenever that is present. The effect upon the cholesterol metabolism is nil. With this operation efficient bile drainage is only possible through a choledochotomy opening.

¹ We are indebted to Drs. Lilienthal, Beer, Berg, Elsbarg and Moschcowitz, chiefs of the surgical services of Mount Sinai Hospital, for their coöperation in these studies.

² These types include: (1) Cholecystectomy with or without drainage of the cystic or hepatic ducts and with or without choledochotomy and drainage of the common duct; and (2) cholecystostomy with or without choledochotomy and drainage of the common duct.

B. The operation of cholecystostomy accomplishes the following objects: (1) It enables one to remove the end-products of disturbed cholesterol metabolism somewhat better than a cholecystectomy without bile drainage. (2) It affords a surgical method, inferior to cholecystectomy, for draining the infected area: this does not guarantee that the source of infection has been removed and healing may take place before this source has completely disappeared; recrudescences of infection may, therefore, be expected and do actually occur. (3) It affords a method of biliary drainage.

The effects of the chief means of operative bile drainage³—drainage into the gall-bladder and drainage into the common and hepatic ducts—may be summarized as follows: (1) With common duct drainage the system is rapidly depleted of its cholesterol bodies. (2) Gall-bladder drainage does not accomplish this extreme effect unless there be a concomitant obstruction in the common bile duct. (3) The rate of drop of the cholesterol in the blood serum varies and depends upon the initial figure and the length of time of drainage; after a certain minimum is reached, there is no further fall in the cholesterol content of the blood. (4) These effects are obtainable only when the operation has been so performed that proper bile drainage is accomplished and all obstructions have been removed from the ducts. (5) When obstruction is present before operation the complete removal of this obstruction is followed by a fall from the preoperative hypercholesterolemia, the figures reaching a normal level very promptly. (6) If the preoperative figure has been low because of an associated high temperature the drop of temperature following operation is accompanied by a rise in the cholesterol content of the blood to the normal level. (7) When the postoperative drop has been large and there had been no antecedent obstruction the fall is partly due to a lipid-free diet.

The effect of bile drainage *per se* upon the underlying metabolic activities whose function is the control of the cholesterol content of the body and blood, is probably nil. What is accomplished is the removal of that portion of the cholesterol which exceeds the normal minimum content. How thoroughly this is accomplished depends upon the severity of the metabolic disturbance and especially upon the completeness or incompleteness of the biliary fistula; and when this is complete, one may see the cholesterol content of the blood fall to values below the usual normal.

It is evident from these facts that a choice of the proper operation, efficiently carried out, combined with the intelligent use of bile drainage, restores the cholesterol content of the blood and bile to the normal. It is evident, too, that the essential cause of the hypercholesterolemia has, probably, not been influenced in any way.

In the present communication the more permanent results of

³ Drainage into the stump of the cystic duct is not efficient.

operation for cholelithiasis are considered. The purpose is the isolation and description of that group of cases with recurrent symptoms in which the dominant element causing the disturbance is some fault in the cholesterol metabolism. At the same time the behavior of the cholesterol metabolism in all of the other cases will also be considered. All of the cases have been grouped as follows:

GROUP I (74 per cent). Cured cases:

1. Infective cases.
2. Cases with slight metabolic disturbance.

GROUP II (26 per cent). Cases with postoperative symptoms:

1. Cases with surgical causes.
 - (a) Old cholecystostomy cases.
 - (b) Cases with strictured ducts.
 - (c) Cases with new and recurrent infections, or persistence of old infection.
2. Stone cases:
 - (a) Infective cases—cholangitis.
 - (b) Diathetic cases.
3. Diathetic cases:
 - (a) Milk cases—easily relievable by diet and not readily recurrent.
 - (b) Severe cases.
 - (a') Diet constantly necessary.
 - (b') With attacks of pain and jaundice.
4. Recurrent pregnancy cases.⁴

The cases in this series were not selected in any way but were studied *seriatim* as they were consecutively admitted and discharged from the hospital. The original studies were made in the latter part of 1914, in 1915 and in 1916. Since then the cases have been followed and the subsequent clinical facts and laboratory findings form the criteria upon which the conclusions of this communication are based. The methods of studying the cases and the technic of the laboratory (blood) examinations were detailed in a previous paper of this series. The descriptions of the individual groups as noted above follow.

Cured Cases. The cured cases form the great majority of all of the cases studied and make up a total of 74 per cent.⁵ It has been possible to distinguish that the cured cases must include: (1) Those initiated by infection; (2) those initiated by disturbances in the cholesterol metabolism; (3) those in which both of these elements have been working together or have consecutively followed one another.

The purely infective cases are the simplest. An infection having taken place the patient was subjected to operation: a perfect recovery was made and the latter has up to the present remained

⁴ The discussion of these cases is reserved for a future occasion.

⁵ *Vide infra*, under recurrent symptoms, for explanation of percentage.

permanent. No postoperative symptoms are expected unless some mechanical disability or purely surgical emergency (for instance, intestinal obstruction) takes place. A number of the cases in this group were jaundiced at the time of the primary operation and a hypercholesterinemia was present; the character of the anatomical findings at operation and the laboratory indications of the subsequent activity of the cholesterol metabolism give sufficient evidence that jaundice had no relation to the latter and was due entirely to obstruction of the bile passages. The notes of the following cases form excellent illustrations of this type of case:

CASE I.—In a woman, aged twenty-nine years, the first attack of right hypochondriac pain occurred five days after the birth of her first child. Jaundice was present. Operation disclosed a gangrenous gall-bladder and the common duct seemed compressed from the inflammatory infiltration. A cholecystectomy was done and common duct drainage was instituted. Prior to operation the cholesterol content of the blood was 250 mg. per 100 cc. A high figure—275 mg. per 100 cc—was present six days later coincident with an increase in the jaundice and probably due to the increase in the inflammatory infiltration produced by the operative trauma. Thereafter as this subsided and the jaundice disappeared the cholesterol content of the blood fell to 140 mg. per 100 cc. This patient has remained cured.

CASE II.—This patient, aged fifty-five years, had had symptoms for six years with frequent attacks of colic. The last attack was accompanied by jaundice and on the third day of the jaundice she was operated upon. The blood contained 235 mg. cholesterol per 100 cc. Operation showed stones in a shrunken gall-bladder, which, microscopically, showed chronic productive inflammation, the ducts were clear. Cholecystectomy without bile drainage was done. The convalescence was uneventful. On the seventh day the cholesterol content of the blood was normal. Four months later the patient reported herself in perfect health; the blood content of cholesterol was normal. This patient, too, is cured.

This group also includes a number of cases in which the character of the anatomical findings indicate a total absence of infection, and the examination of the concretions show that these contain from 90 to 100 per cent of cholesterol; both of these facts show almost conclusively that prior to the primary operation, at least one period had occurred in which a hypercholesterinemia was present and that the latter had been reduced to the normal by a precipitation of one or more stones. At the time of operation a hypercholesterinemic state was not present as its causative factor was inactive. The course of affairs subsequent to operation has not included any

new hypercholesterinemic crisis—physiological or other—and the patients have remained cured. The following case illustrates:

CASE III.—This woman, aged thirty-three years, married for one and a half years had had symptoms characterized by attacks of abdominal cramps with vomiting. The physical examination was negative and there was no hypercholesterinemia. Operation showed an anatomically normal gall-bladder containing a single stone of a soap-like translucency and composed entirely of cholesterol. The cholesterol content of the blood remained normal after discharge from the hospital and the patient is cured. The initial cause of the hypercholesterinemia in this patient was probably that associated with pregnancy.

In other similar cases a hypercholesterinemia was present at the time of operation. Drainage having been instituted, the excess of blood cholesterol was removed. Case IV shows that in the post-operative course of such patients the blood content of cholesterol can remain normal; this fact distinguishes this group from one subsequently to be described in which a return of the hypercholesterinemia is associated with the appearance of symptoms.

CASE IV.—A married woman, aged twenty-seven years, was operated upon at the subsidence of the third attack of cholecystitis. Prior to operation the blood contained 200 mg. of cholesterol per 100 cc. A cholecystectomy was done and bile drainage was instituted. The changes in the cholesterol metabolism immediately following operation were as follows:

	Blood cholesterol, mg. per cent.	Bile cholesterol.		Choluria.	Stools.
		Cc.	Mg. per cent.		
June 27	225	0.158	None	Acholic.
" 28	0.125	..	0.062	None	Acholic.
" 29	25	0.425	None	Acholic.
" 30	65	0.515	None	.
July 1	17	?	None	Colored.
" 2	0	...	None	Colored.
" 18	0.195				

In March of the following year the woman reported herself to be in good health without symptoms of any kind. The blood contained 0.12 gm. of cholesterol per 100 cc.

The largest proportion of the cured cases are composed of those in which the operative findings and the laboratory examinations indicate that prior to operation the pathological process had included both infection and disturbances of the cholesterol metabolism. Depending on conditions present, a hypercholesterinemia was, or was not present at the time of operation and bile drainage was

either instituted or omitted by the operator. The absence of any symptoms in the further clinical courses of these patients indicates that the line of treatment was the correct one in the individual case and that the tissues and the metabolic activities are restored to the normal. The following cases illustrate:

CASE V.—A woman, aged forty-eight years, had had two attacks of gall-bladder colic in the six months preceding operation. At the time of operation she was not jaundiced, although there was some bile in the urine; the blood contained 0.1925 gm. of cholesterol per 100 cc. A cholecystectomy was done. The gall-bladder showed slight chronic inflammatory changes and the bile contained some gravel. There was some tendency to diarrhea after the patient left the hospital but otherwise she was symptomless; at the end of two months the cholesterol content of the blood was 135 mg. per 100 cc; the cure has remained permanent.

CASE VI.—In a woman, aged fifty-nine years, operation showed a gall-bladder with much productive inflammation in its walls and with much pericholecystitis. Stones were present in the gall-bladder but the ducts were free. Symptoms had been present for one year; jaundice, however, had never been present. Prior to operation the cholesterol content of the blood was 297.5 mg. per 100 cc. A cholecystectomy was done. Seven months after the operation the patient reported herself to be symptom-free and the cholesterol content of the blood was 197.5 mg. per 100 cc.

CASE VII.—In a woman, aged twenty-six years, right hypochondriac pain without jaundice, vomiting or other symptoms had been present for three years. The blood contained 200 mg. cholesterol per 100 cc. A cholecystectomy was done. The gall-bladder was found to be full of stones and its wall showed productive inflammation. Eight months after operation the patient reported that the symptoms were entirely relieved. The cholesterol content of the blood at that time was 136 mg. per 100 cc.

Cases with Postoperative Symptoms. In the series of 115 cases, postoperative symptoms of one kind or another were present in 26 per cent. We include in this group all kinds of cases, those with mild symptoms—which, according to our studies have an important significance—as well as those with the more severe manifestations necessitating secondary operations. In the reports usually found in the literature only those are recognized which must be operated upon again and in one of the latest communications the number of such is put at 8.5 per cent (Deaver). In the series which we have studied the number of reoperation cases corresponds with this figure and forms about 10 per cent of the total.

A number of communications have been published in the last few years by Eisendrath, Deaver, Judd and Harrington, Deaver and Reimann, and Davis which fully describe the cases in which the postoperative symptoms have been sufficient to require secondary operation. The actual indication for the latter, whether fistula, stone, cholangitis or obstructive jaundice, is of a purely mechanical or surgical nature and the condition as such bears very little, and then only indirectly, on the disturbances of the cholesterol metabolism, except in those stone cases in which it can be definitely proven that the calculi, which are subsequently found in the ducts, were formed since the primary operation. The purely surgical aspects of these conditions have been very amply discussed by the various men mentioned and the discussion needs no repetition here. Wherein these surgical conditions, especially the repeated or continual reformation of stones subsequent to operation, have relationships with disturbances of the cholesterol metabolism, is a topic that we propose discussing on another occasion.

In 16.5 per cent of the cases in our series (64 per cent of those with postoperative symptoms) the dominant and sole cause for the recurrence of symptoms is an underlying disturbance of the cholesterol metabolism. In other series studied elsewhere, such as those indicated previously—Eisendrath, Deaver, Judd, and others, this subject receives no attention and in the majority the symptoms are dismissed as being too mild for special consideration or as being, perhaps, one of the unavoidable sequelæ of an abdominal exploration and operation; at other times the cause is frequently assumed to be "postoperative adhesions." In the severe cases it is most frequently assumed that the symptoms are due to the retention or reappearance of stones in the biliary ducts.

In all of the cases in this group, whether the symptoms be mild, or whether they be severe, a hypercholesterinemia is constantly found. In about two-thirds of the cases the symptoms are very mild, or only moderately severe and the disorder is fairly easily and sometimes permanently controllable by dietetic means. In the remaining third the symptoms are very severe; a cure is difficult to attain by medical means alone and the treatment must be constantly adhered to; relapses are frequent and severe; and operation is on occasion imperatively demanded.

The essential part of the medical treatment is the adherence to a diet from which substances containing fats and lipid bodies are excluded. The latter include the ordinary fats and butter, cream and the yolks of eggs, the roe of fish and certain fish which are rich in fat, such as salmon and sturgeon, oils, nuts and certain vegetables and fruits such as the olive. In severe cases the restriction in diet must be fairly extreme: the patient is apt to tire very quickly, to rebel and to demand a more liberal choice of food articles. With the more intelligent group of patients, the benefits which quickly

make their appearance are very satisfying and the discomfort of a restricted diet is more or less willingly tolerated. In the others the patient's discontent with the restricted diet must be relieved by permitting on one day of the week a wider choice; with practically all patients this measure suffices.

In the mild cases the symptoms become prominent more because of their persistence and constant presence than because of their severity. Usually there is a dull pain or ache in the region of the liver, or a sense of vague discomfort, described frequently as a bloated feeling. Occasionally the pain gravitates downward toward the iliac fossa. The bowels show a tendency to be constipated. The symptoms are frequently referred to the stomach. The physical findings show no abnormalities. It is difficult to make out any enlargement of the liver: in many the results of the operation have, because of the presence of massive adhesions, fastened the free edge of the liver down in the neighborhood of the scar and it is not possible to say that the liver edge, which is palpable, indicates displacement or some enlargement. The liver is not tender in the mild cases. There is never any jaundice.

In the mild cases the blood examinations show a moderate hypercholesterinemia. The figures in our cases have varied from about 200 to 300 mg. of cholesterol per 100 cc of blood.

After a thorough cleansing of the intestinal tract and some attention to the diet along the lines previously indicated, the symptoms are quickly relieved. The cholesterol content of the blood returns to its normal variations. The following is an illustrative case:

CASE VIII.—In June, 1915, a woman aged forty-eight years, had been operated upon and a very adherent, small and contracted gall-bladder had been removed. A good recovery having been made she was discharged from the hospital. In September 1915, the patient returned and stated that her symptoms had not been relieved; at this time her blood contained 205 mg. of cholesterol per 100 cc. The patient was instructed as to her diet. In November 1915—one month later—she reported that she was feeling much better: she was directed to persist in the diet and to return for observation at regular intervals. In March, 1916, the notes read that the pain and other symptoms had been entirely relieved: the blood content of cholesterol was normal at this time—162 mg. cholesterol per 100 cc of blood.

This group includes cases in which both cholecystectomy without biliary drainage was done and those in which efficient biliary drainage was obtained. The previous case was not drained. In the following case biliary drainage had been instituted:

CASE IX.—A woman, aged fifty-six years, was operated upon in the first attack of cholecystitis of which a prominent symptom was jaundice. Prior to operation the blood contained 237 mg. of chole-

terol per 100 cc. The findings at operation included an empyema of the gall-bladder, a pericholecystitic abscess, and stones in the common bile duct. Cholecystectomy and choledoschotomy were done and common duct biliary drainage was instituted. The condition of the cholesterol metabolism during the convalescence is shown in the table:

		Blood cholesterol, gm. per cent.	Bile cholesterol.		Choluria.	Stools.
			Cc.	Mg. per cent.		
June	25	..	270	0.140	None	Acholic.
"	26	..	130	0.136	None	Acholic.
"	27	..	130	0.085	None	Acholic.
"	28	0.137	245	0.106	None	Acholic.
"	29	..	220	0.120	None	Acholic.
"	30	..	160	0.115	None	Acholic.
July	1	..	320	0.115	None	Acholic.
"	2	..	240	0.118	None	Acholic.
"	20	..	Fistula closed		None	Colored.

Two months later the patient reported some indefinite discomfort in the upper right quadrant. The blood contained 272 mg. of cholesterol per 100 cc of blood. She was given proper directions concerning the diet and was told to report again after one month's time. At the latter time she was symptom-free and her blood contained only 0.185 gm. cholesterin per 100 cc of blood.

In the severer cases the symptomatology is similar; pain, however, is more prominent. The pain is located on the right side of the abdomen high up over the liver region. It is fairly constantly present and is persistent; its intensity is variable but is usually not extreme. No enlargement of the liver can be made out; the liver is usually not tender; jaundice is not present. The notes of Case X are illustrative.

CASE X.—In a married woman aged thirty-five years, a cholecystectomy without bile drainage had been done for a dilated gall-bladder packed full of stones. One year later the woman reported that she was having attacks of cramps almost every four weeks without vomiting, jaundice or fever: the attacks always subsided spontaneously. The blood contained 2875 mg. of cholesterol per 100 cc. During the following year it proved difficult to keep her free of symptoms (sometimes it was impossible to make her follow directions) and a year later she still reported having similar symptoms; at that time the blood contained 237 mg. cholesterol per 100 cc.

It is very likely that if this patient had received the benefit of a prolonged biliary drainage that much more could have been accomplished with the dietetic measures.

In a number of patients belonging in the last group the clinical course is distinguished by the periodical or irregular occurrence of

very acute attacks referred to the right hypochondriac quadrant in which pain, similar in all respects to that of a severe biliary colic, vomiting and varying grades of jaundice form dominant features of the symptom-complex. In all of these marked degrees of hypercholesterinemia are demonstrable. Occasionally these sharp attacks are associated with chills and fever. In most of the cases a spontaneous disappearance of the symptoms takes place.

At first sight the assumption is almost invariably made that the patients are suffering from a persistence, or reformation of stones which are attempting to pass from the biliary passages. Under this impression several patients were subjected to secondary operations, and yet these explorations demonstrated that the bile passages were clear of concretions, that the ducts were widely dilated and contained a turbid bile, and that no gross lesion existed in any of the neighboring organs, especially in the pancreas. In these cases bile drainage was necessarily instituted at the operation and during the convalescence this was followed by a reduction of the cholesterol content of the blood. After recovery and discharge from the hospital the clinical course assumed similarities to those of the patients in the immediately preceding group, with the exception that the efficient control of the condition was much more difficult to attain and make permanent. In one of the patients attacks of severe pain were present at periods subsequent to each of several secondary operations apparently due to the marked disturbance of metabolism and the insufficient effect of the rigid exclusion of lipoid bodies from the diet.

The notes of the following case illustrate this type of case.

CASE XI.—This married woman was admitted to the hospital on the service of Dr. A. G. Gerster in 1912. At that time the history stated that she had three attacks of pain in the right hypochondrium with jaundice and chills and fever: the last attack occurred four weeks previous to her admission. At operation one stone was found in the gall-bladder and several in the common bile duct; the bile itself was thick and grumous. A cholecystectomy was done and the hepatic duct was drained. The microscopical examination of the gall-bladder showed chronic inflammation. After a fairly uneventful convalescence she was discharged from the hospital.

Three years later, in 1915, she was readmitted to the medical side of the hospital on the service of Dr. Brill. The patient had been well until four weeks before admission when another attack of gall-bladder colic had occurred and had been accompanied by jaundice. Under conservative treatment she made a spontaneous recovery and was discharged from the hospital.

Two weeks after the last discharge from the hospital, the patient was admitted for the third time to the surgical side on the service of Dr. Elsberg. The symptoms had again returned. Under observation in the hospital a very severe attack of colic occurred and

within twenty-four hours the skin became distinctly jaundiced. The patient was therefore explored for the second time. The operative findings included: (1) A common bile duct dilated as large as one's finger; (2) a yellow bile containing numerous flakes; (3) *the absence of any concretions* in any part of the biliary passages. The common bile duct was drained.

We were just at the beginning of our studies at this time and the patient was brought to our attention at this stage of her history. Our first blood examination was made three days after operation, in the presence of a freely draining, complete common duct biliary fistula, and showed that the patient's blood contained 280 mg. cholesterol per 100 cc. Under the indicated circumstances the probabilities are almost certain that prior to operation the patient's cholesterol metabolism was most profoundly disturbed and that the amount of cholesterol in the blood was very much higher. The further study of the cholesterol metabolism during the healing of the wound and the convalescence was as follows:

			Blood cholesterol, gm. per cent.	Bile cholesterol.	
				Cc.	Gm. per cent.
Feb.	18	0.280		
"	19	?	0.071
"	20	?	0.11
"	21	0.103		
"	23	?	0.092
"	24	?	0.087
"	25	0.155	?	0.120
"	26	?	0.132
"	27	?	0.075 ¹
"	28	0.100	?	0.068
Mar.	5	0.09575		
"	10	0.130		

On February 28 there was an insignificant amount of biliary discharge: within a few days the sinus closed entirely. On March 12, when the patient was discharged, the sinus was well healed, and the patient was relieved of all symptoms. We realized that this would be one of the cases in which diet would be very necessary if one hoped to have the absence of symptoms remain permanent. The patient was therefore given full directions and was instructed to report at regular intervals for blood examinations. During the following year the latter showed the following results:

April 22, 1915	. .	No symptoms.	Blood = 0.1625 per cent cholesterol.		
May 5, 1915	. .	" "	" = 0.1875	"	"
" 20, 1915	. .	" "	" = 0.1875	"	"
June 4, 1915	. .	" "	" = 0.1550	"	"
Sept. 16, 1915	. .	" "	" = 0.1750	"	"
Nov. 4, 1915	. .	" "	" = 0.1735	"	"
Feb. 9, 1916	. .	" "	" = 0.1500	"	"
April 26, 1916	. .	" "	" = 0.1480	"	"
May 26, 1916	. .	" "	" = 0.1700	"	"

With the exception of some functional symptoms referable to the ménopause.

We did not see the patient after that until 1919. At that time she reported that she had been in good health for the entire time. At this time her blood contained 0.176 gm. of cholesterol per 100 cc.

Cases of this kind, while, perhaps, relatively few in the total number of cases seen, are most satisfactory. In order to obtain good results it is necessary that one have complete coöperation on the part of the patient in the matter of diet. In an extreme case of this kind the effect of the initial depletion of lipid bodies from the body is most valuable in that it restores the body content of cholesterol to relatively normal proportions; then with proper dietary regulations the latter can be kept within its normal limits.

Conclusions. 1. The diathetic factor in the formation of gall stones has been greatly neglected.

2. The diathetic factor is an important cause in the recurrence of symptoms after operations.

3. The recognition of this diathetic factor is important in the treatment of cases of cholelithiasis both before and after operation.

THE USE OF SULPHUR IN THE TREATMENT OF ARTHRITIS DEFORMANS.

BY HOBART A. REIMANN, M.D.,

AND

GEORGE W. PUCHER, PH.D.,

BUFFALO, N. Y.

(From the Buffalo General Hospital.)

IN 1907, Bory,¹ and Delahaye and Piot² administered subcutaneous and intramuscular injections of sulphur in glycerin or olive oil, for the treatment of a variety of conditions, such as, bronchopneumonia, pulmonary tuberculosis and arthritis. Since then, occasional clinical reports, favorable and unfavorable, have appeared in the literature concerning the use of sulphur for arthritis and various painful muscle conditions.^{3 4}

In 1921 and 1922, Meyer-Bisch⁵ published rather extensive papers on this subject, in which both chemical and clinical data are presented. This investigator reports remarkable recoveries and improvements of cases of arthritis deformans after a course of intramuscular injections of sulphur in olive oil.

We have studied the effect of sulphur in a number of cases of joint affections classed with arthritis deformans, including in our

studies roentgenographical observations on the affected joints. Since, in arthritis deformans, there is probably a disturbance in cartilage metabolism, it is perhaps not illogical to study the relation of sulphur, which forms so large a percentage of the constituent of cartilage, to that disease. Indeed its importance is even more emphasized since the fundamental work of Hopkins,⁶ which demonstrated the activity of sulphur compounds in oxidation and reduction processes. Moreover the recent publication of Haggard,⁷ showing the ease and rapidity with which sulphides and elemental sulphur are oxidized in the blood, would seem to make the study of the influence of that element upon the metabolic processes of cartilage and muscle of particular importance. Experiments upon the fate, chemistry and pathology of parenterally administered sulphur, have therefore been undertaken by the writers.

Our study, comprising a number of cases of arthritis deformans shows that, although in a certain number of cases, as seen in a table given below, improvement was distinct, yet in none of these cases were we absolutely certain that this improvement was due to a specific action of sulphur, and that similar results could not have been obtained by non-specific protein injections. In no case did the roentgen-ray plates reveal any changes in the condition of the joints involved.

Our results rather seem to justify the conclusion of Hirsch and Sternberg⁸ regarding the action of protein treatment and similar therapy. They regularly observe a certain number of surprising results whenever introducing any new preparation. They believe that this is due simply to mobilization of the psychic reserve powers, under the influence of a strong stimulus and of fever. Such cures last for a few days or months, according to the energy of the patient. The individual constitution influences the action of stimulating treatment, especially the fever, more than the preparation used.

Clinical. Preparation of the sulphur used: Flowers of sulphur, 7 mg. to 1 cc, were dissolved in olive oil, free from fatty acid, and sterilized at 150° C. for two hours. Longer heating was avoided, as it turns the solution to a deep red color due to the reaction of the sulphur with olive oil or some of its decomposition products. The final product, as used, was a clear, golden yellow liquid.

Method of injection: The above solution was injected intramuscularly in the gluteal region, starting with 1 cc (7 mg.) and repeated at five- to seven-day intervals, increasing the amount by 1 cc each time until 7 or 8 doses were given.

Character of the reaction: The severity of the reaction to the injection was a rather individual one, particularly regarding the temperature. Some of the patients showed no increase of temperature, even following doses of 6 cc (42 mg.). Most of the patients, however, responded with nausea, vomiting, chills, restlessness,

general joint pains, and severe headache. The headache was often relieved by pyramidon. With the larger doses of sulphur, there was severe pain at the site of injection, lasting for several days. The pain in several cases was so severe that it required the administration of sedatives. That all these phenomena were not due to the action of olive oil was shown by the fact that control injections of olive oil by itself produced no reaction.

The result of the clinical study of 17 cases of arthritis deformans treated by the method described is presented below in tabular form. (See Table I.)

Of the 17 cases observed, 4 showed marked improvement and 4 slight improvement. The remainder were either not benefited by the treatment, or became actually worse. Even in the markedly improved cases no demonstrable changes were shown roentgenographically after treatment.

In a few of the cases, also, the blood cells were counted, and in accordance with the findings of Meyer-Bisch we have satisfied ourselves that simultaneously with the constitutional reaction there is an increase in the polymorphonuclear leukocytes (up to 24,000). We have not, however, been able to confirm the findings of Meyer-Bisch on the reduction of hemoglobin and erythrocytes.

The following cases, though included in the table, seem of especial interest and are reported more fully.

CASE I.—H. B., aged fifty-two years, complained of pain in most joints and deformity.

Two previous admissions to the hospital with the same complaint, for the purpose of tonsillectomy, massage, and other treatment, resulted in no improvement. Mental apathy and depression was very marked. The patient had heard of the new sulphur treatment and returned a third time to try that. He had become progressively worse since last discharged from the hospital and reentered the hospital a bedridden patient totally unable to move about. No active or passive motion of his extremities was possible without severe pain. The jaws could not be separated more than a half inch. There was marked deformity of most joints and considerable muscle atrophy. He weighed 85 pounds. Roentgen-ray examination showed nothing more than a decrease of bone density which results from non-use.

From October 17 to November 28, 1922, he received at intervals of five to seven days 5, 10, 15, 21, 28, 35, 42, and 49 mg. of sulphur successively. After every injection the patient complained of increased pain in his joints, headache and tinnitus. The injections were followed in eight to twelve hours by a temperature of 100° to 101° F., lasting a day or two. There was considerable soreness at the site of each injection.

TABLE NO. 1.

Case No.	Name, Hosp. No., Age.	Duration, years.	Joints involved.	Deformity.	Previous treatment.	Complications.	Temperature.	Dose in mg.	Reaction.	Final result.
I	H. B. 139010 52	2	Almost all joints of the body	Marked periarticular deformities; roentgen-ray shows lack of density; muscle atrophy marked	Tolysin; cinchophen; baths; tonsillectomy; extraction of teeth	Mental depression at time of admission	Optimistic; cooperative	5, 10, 15, 21, 28, 35, 42, 49	Severe after 21 mg. and the higher doses	Marked improvement; gained 35 pounds.
II	S. W. 138599 61	?	Wrists, ankles, knees, shoulders, fingers	Slight periarticular thickenings	None	Chronic bronchitis	Neurotic	5, 10, 15, 21, 28, 35, 42	Slight; pain in joints and headache	Not improved.
III	R. H. 139322 13	2	Wrists, hands, knees, elbows	Marked periarticular deformities; roentgen-ray shows lack of density; muscle atrophy and contractions	Tonsillectomy; salicylates; extraction of teeth	Secondary anemia	Not peculiar	7, 14, 21, 28, 35	Headache; pain in joints and at site of injection	Marked improvement; gained 25 pounds.
IV	C. J. 139908 25	6	Ankles and feet	Marked periarticular swelling	Salicylates; baking; plaster casts	None	Not peculiar	14, 21, 28, 35, 42, 49, 56, 70	Very severe after 42 mg.; vomiting and chills; pain in all joints excepting deformed ones	Marked improvement; walks with out difficulty.
V	E. P. 141428 21	3	Wrists, (right) shoulder, and ankles	Roentgen-ray shows a slight irregularity of the articulating surface of right radius; uneven density carpal bones of right wrist	None	Supervention of diabetes mellitus during the course of treatment	Not peculiar	21, 35, 42, 35; 5 cc milk	Moderate	Slightly improved; walks better.
VI	M. S. 140983 57	11	Almost all joints of the body	Marked deformities; bone changes, muscle contractions, atrophy	None	None	Non-coöperative	7, 14, 14, 7, 21, 28, 35	Severe	Not improved.
VII	D. H. 140190 50	5	Elbows, knees, shoulders, feet	Roentgen-ray shows lack of density; periarticular thickenings	Tonsillectomy; arthromy of right knee; salicylates; massage	None	Not peculiar	7, 21, 28, 35, 42, 49, 42	Mild	Considerably improved; can walk more easily and with less pain.

VIII	A. S. 131124 28	4	Knees, ankles, hips, left el- bow, wrist and hand	Bone changes and peri- articular deformities; muscle contraction and atrophy	Tonsillectomy; teeth extracted; pro- teogen; vaccines; salicylates; toly- sin, cinchophen	None	Optimistic	5, 10, 28; 6 cc plain oil; 42, 35, 21	Very severe; no reac- tion with plain oil	Slightly less pain.
IX	L. D. 136663 55	?	Almost all joints of the body	Bone changes of wrists and hands and muscle atrophy	Cinchophen	Advanced arter- iosclerosis; an- gina pectoris	Apathetic; non-cooper- ative	7, 14, 28, 35, 42, 49	Very slight	Not improved; de- formity progress- ing.
X	S. O. 137362 52	5	Wrists, hands, shoulders, el- bows, knees	Periarticular swellings; roentgen-ray shows a roughening of the ar- ticular surfaces of the knee-joints	Salicylates; proteo- gen; diet; heat; vaccines	None	Optimistic	5, 10, 15, 21, 28, 35, 42, 49 Second course 2 mos. later: 21, 28, 35, 35, 35	Mild	Slightly improved; pain less severe.
XI	M. D. 145237 48	2	Almost all joints of the body	Marked periarticular de- formities; roentgen- ray shows bone de- struction and hyper- trophy	Salicylates; tonsil- lectomy; vaccine; proteogen	None	Optimistic	7, 14, 28, 35, 42, 49, 56, 63, 28; 5 cc milk; 8 cc milk; 10 cc milk; 14, 14	Severe with sulphur, less severe to milk	Condition worse; progressive de- formity and in- capacitation.
XII	L. B. Out pat. 17	7	Almost all joints of the body	Marked periarticular de- formities	Salicylates; tonsil- lectomy; vaccine; massage	Secondary ane- mia; melan- cholia	Very depress- ed; non-co- operative	7, 10, 14, 21, 28	Mild	Not improved.
XIII	J. B. Out pat. 65	15	Almost all joints of the body	Marked periarticular de- formities and bone changes	None	Arteriosclerosis	Non-coopera- tive	7, 10	Mild	Not improved.
XIV	M. K. Out pat. 50	7	Elbows, knees	Slight periarticular thick- enings; roentgen-ray shows absorption of cartilage of left knee- joint	None	None	Optimistic	7, 21, 35, 42, 42, 49, 35, 49	Severe after 42 mg.	Considerable im- provement for 2 months.
XV	J. S. Out pat. 44	12	Almost all joints of the body	Slight thickening of most joints	None	None	Not peculiar	7, 21, 35, 42, 42, 49, 35, 49	Moderate	Improvement for 2 months.
XVI	M. W. Out pat. 38	2	Knees, ankles, right elbow	Slight thickening	Salicylates	None	Not peculiar	7, 14, 14, 28, 35, 42	Considerable; no chills	Marked improve- ment; much less pain.
XVII	J. P. Out pat. 42	3	Knees, hands, shoulders	Slight deformity of the knuckles	Salicylates	None	Not peculiar	7, 14, 14, 21, 28, 35, 42	Quite severe; no chills	Not improved.

Some improvement was noticed after the fifth injection, and from then on, the improvement was rapid. With the coöperation of the patient, physical therapy in the form of exercise and massage was rigidly enforced. The change in the patient's mental attitude, to one of optimism and coöperation was very striking and probably was a great factor in his recovery. In two months from the beginning of the treatment the patient was able to dress himself and walk a few steps. He was discharged April 7, markedly improved. He weighed 115 pounds. Roentgen-ray pictures at discharge showed no variation from those taken at admission. Eight months later the patient was able to walk without any stiffness or pain and felt very well; he then weighed 120 pounds. Periarticular deformity, however, was still present.

This case is an excellent example of the cures reported by various authors and tacitly ascribed to the effect of the drug employed, in the case of Meyer-Bisch to sulphur. Yet there is no ground for belief that any organic interference with the motion of the joints has in any way been eliminated, as the roentgen-ray plates show absolutely no difference in the appearance of the joints and whatever deformity was present previous to the "cure" is still present.

CASE III.—R. H., a girl, aged thirteen years, complained of pain and deformity of joints.

Her present illness started like an attack of acute rheumatic fever two years ago. Although she apparently recovered from the acute attack, she noticed that her joints began to swell and ache. Tonsillectomy was performed at that time with no relief. The wrists, knees and hands became progressively worse so that she became bedridden.

Upon admission to the hospital there was marked deformity of both wrists, hands and knees, with severe pain on active or passive motion. There was considerable muscle contraction and atrophy. Her temperature was 100°F. Roentgen-ray showed no evidence of bone disease excepting the characteristic lack of density and some indistinctness of outline of some of the phalangeal joints.

The patient received six doses of the sulphur (in solution) as follows: 7, 14, 21, 21, 28, and 35 mg. intramuscularly at weekly intervals; but after the third dose the pain at the site of the injection, was so severe that for a time the patient refused further treatment. However, after the first injection an improvement was noticed which has continued to nearly complete recovery. When last seen, seven months after starting the treatment, the patient had gained about 25 pounds and was walking about freely, without any pain or discomfort. There is still some thickening around the joints which were affected. Roentgen-ray examination at this time revealed no visible changes in the bones.

Here, too, the effect was striking in spite of the negative radiographic findings. However, psychological factors probably had very little to do with this case.

CASE IV.—C. J., a man, aged twenty-five years, complained of pain and "swelling" of the ankles.



FIG. 1.—Case 3. R. H., photograph of hands showing swelling in the second phalangeal joints of the first and third fingers of the right hand before treatment.

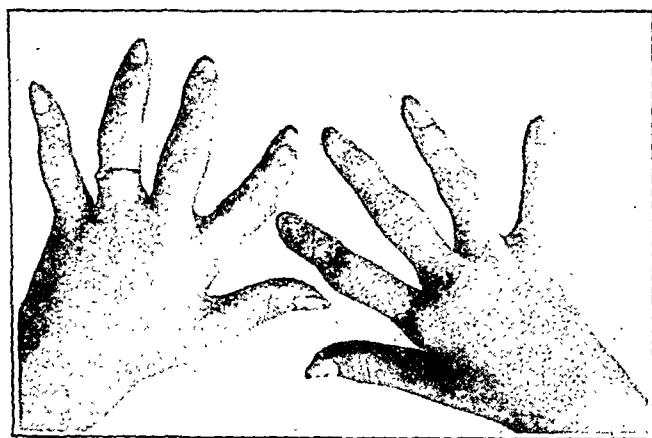


FIG. 2.—Case 3. R. H., photograph of hands showing reduction of swelling in the joints after treatment.

The trouble began in 1917 with pain and swelling of his toes and feet which finally spread to the ankles. The condition has never affected any other joints and has become progressively worse until walking became impossible on account of the pain and thickening. Two months before admission to the hospital his feet were placed in plaster casts with slight relief of pain. Between November 28, 1922, and February 6, 1923, the patient received 14, 21, 28, 35, 42, 49, 56, and 70 mg. of sulphur. After the fourth dose the patient reacted severely to each injection in proportion to the amount



FIG. 3.—Case 3. R. H., roentgenogram of hands showing periarticular swelling in second phalangeal joints of first and third fingers of the right hand before treatment.



FIG. 4.—Case 3. R. H., roentgenogram of hands showing reduction of periarticular swelling of the joints after treatment.

injected. Reactions consisted of chills, temperature of 100.5° F, vomiting, pain at the site of the injection, and, curiously enough, pain in all joints excepting in the diseased ones. After the fifth injection the pain began to abate and the swelling to disappear and

April 4 the patient was discharged improved, free from pain or deformity. Four months later he was able to walk freely and has been able to resume his work.

One cannot definitely say that sulphur did not have an influence on the diseased joint tissue in this case. The recovery is certainly noteworthy considering the comparatively long duration of the disease.

CASE XI.—M. D., a woman, aged forty-eight years, complained of swelling and stiffness of all joints excepting the hips.

Present illness: In 1921 her hands became swollen and painful and soon after her knees, shoulders, elbows and feet became involved. The condition gradually progressed until admission to the hospital, at which time walking was possible only with the greatest difficulty, due to stiffness and pain.

The patient looked forward to the sulphur treatment with greatest hope. She received 7, 14, 28, 35, 42, 49, 56, and 63 mg. of sulphur between January 12 and February 28, 1923. The most distressing features of the reactions in this case, were severe headache and pain at the site of injection.

In spite of coöperation on the patient's part, there was no improvement in locomotion or in the amount of pain, so that in March, 5 cc, 8 cc, and 10 cc of sterile milk were injected intramuscularly at five-day intervals. The reactions were identical, subjectively, to those produced by sulphur, excepting that they were not as severe and the pain at the site of the injection was not so intense.

The patient was discharged in May, unimproved, and readmitted in June when walking had become impossible. At this time the roentgen-ray plates showed partial destruction of the ends of some of the metacarpal bones, lipping of the patella, peculiar density of the articulating surfaces of the condyles of the femur, and irregularity in the outline of the astragalus and lower end of the tibia.

This case illustrates the futility of the sulphur treatment in the presence of organic hindrance to the activity of the joint even though the patient coöperated in every way.

Metabolism. In this work we desired only to test the main conclusions of Meyer-Bisch and so only a small amount of quantitative data has been collected.

Meyer-Bisch concludes that the output of urine after a sulphur injection is diminished and that there is a decided retention of chlorids. In 6 cases studied it was found that the volume of urine eliminated after the sulphur injection was subject to about the same fluctuation as before injection. Of course, when the patient developed a high temperature, there was a temporary retention of urine for about twenty-four hours. The chlorid elimination was studied under very carefully controlled diet, so that the salt output and intake could be measured. It was found that, in general, sulphur did not

cause an appreciable retention of chlorids aside from that to be expected from normal fluctuations of urine volume. It is very important to remember that the elimination of chlorids is extremely dependent on the urine volume, and that even in normal patients small fluctuations of urine volume produce large differences in salt output. The chlorid metabolism of one of our patients (A. S.) is presented in full to illustrate the above statements.

TABLE NO. 2.—CHLORINE METABOLISM. CASE A. S.

BEFORE SULPHUR.

Date.	Volume of urine, cc.	Specific gravity.	NaCl received, gm.	NaCl excreted, gm.
Oct. 28 . . .	1340	1.014	11.65	9.55
" 29 . . .	660	...	12.05	5.16
" 30 . . .	740	1.022	11.90	7.15
" 31 . . .	1220	1.008	11.50	9.68
Nov. 1 . . .	540	1.018	12.00	11.05 (?)
" 2 . . .	600	1.026	11.80	6.95
" 3 . . .	480	1.028	11.50	6.00
				(Blood NaCl, 510 mg. per 100 cc)
" 4 . . .	1020	...	12.1	8.15
" 5 . . .	1500	...	11.80	10.60
" 6 . . .	920	...	12.00	6.40
Total . . .	9020		Average NaCl received in one day, 11.83 gm.	Average NaCl excreted in one day, 8.06 gm.
Average urine volume for one day, 902 cc.				

AFTER SULPHUR.

Nov. 7 . . .	920	1.024	0.65	10.30
" 9 . . .	960	...	9.96	(28 mg. sulphur) 3.40
" 12 . . .	1020	1.016	10.90	5.05
" 13 . . .	920	1.014	7.90	4.80
" 16 . . .	420 (?)	1.030	6.40	5.65
" 17 . . .	680	1.028	6.54	8.28
" 18 . . .	580	1.020	2.98	5.95
				(42 mg. sulphur) 5.06
" 19 . . .	620	1.026	6.87	(Blood NaCl, 514 mg.) 5.65
" 20 . . .	1300	1.018	7.90	7.20
" 21 . . .	1200	1.018	8.54	
Total . . .	8580		Average NaCl received in one day, 6.86 gm.	Average NaCl excreted in one day, 6.13 gm.
Average urine volume for one day, 858 cc.				

It will be noted that the average volume of urine per day before injection of sulphur was 900 cc, and for the same number of days after sulphur injection was 858 cc. This slight difference was insufficient to draw the conclusion that sulphur influences the urinary output. The other cases studied gave results similar to those recorded above.

In regard to the chlorid excretion, the great fluctuation of chlorid excretion with volume changes in the normal is strikingly

illustrated. This variation of chlorid excretion has been studied in a large number of normal individuals and in judging chlorid retention must be carefully considered. It will, moreover, be observed that the patient during the first twenty-four hours after injection of sulphur, instead of putting out less chlorid, actually eliminated a much larger quantity than was ingested. In fact when the amount of salt excreted for the normal period and sulphur period is compared with the amount ingested during these periods, it will be seen that the sulphur injection has actually increased and not diminished the chlorid volume (see Table 3). It will be noted that there

TABLE NO. 3.

	Normal period.	First injection.	Second injection.
NaCl ingested	106.2	73.1	26.3
NaCl excreted	69.3	49.1	24.9
Per cent excreted	43.0	67.0	91.0

was no change in the blood chlorid before or after the sulphur injection. This is evident from Table No. 2.

Meyer-Bisch states that after the injection of sulphur, a substance which is probably paired glykuronic acid is excreted. The urine of 6 patients was carefully examined polarimetrically, spectroscopically and by color reactions (phloroglucinol, resorcinol) for glykuronates over three to six sulphur injection periods. At no time could any glykuronates be detected polarimetrically, nor was the resorcinol or phloroglucinol reaction stronger than obtained from patients during normal periods. We have not been able therefore, to confirm the observation that sulphur injections cause excretion of substances giving the reaction of conjugated glykuronates and that they produce changes in the blood chemistry. There is some evidence, which is not yet conclusive, that there is a considerable diminution in the oxygen content of the blood. Thus, in 2 cases the oxygen content was reduced 21.4 per cent and 14.4 per cent respectively. The carbon-dioxide capacity remained the same.

Summary. From a review of the cases reported and the table given, it is clear that only those patients were favorably affected by the sulphur injections who showed radiographically no organic obstruction to the joint motions. The other patients, in spite of coöperation and favorable psychic influence, showed no improvement whatever; so that it is evident that sulphur cannot be looked upon as a remedy for the latter class. The question remains, however, if sulphur might have some value in the other class of cases, and if so, if its action is a specific one or not. Judging from the marked improvement of some of our patients we can understand the enthusiasm of Meyer-Bisch and others for the remedy in arthritis deformans, if indeed the class of cases remedied by sulphur could be classified with that disease. Our observations rather tend to

confirm the efficacy of sulphur in these cases; and it is not impossible if given further trial that the remedy will find its place among others for the treatment of just such kinds of joint affections, whatever they may be. Also, the absence of radiographically demonstrable abnormalities in the joints cannot exclude the possibility of the presence of some organic lesion which might after all be influenced by sulphur, although we have nothing to substantiate this.

It is however another question whether the action of the sulphur in these cases is a specific one. A number of other substances, as is well known, have been used for the treatment of arthritis, as for instance, injections of milk, sanarthrit, proteogen, and vaccines, all of which have been used, according to some observers with favorable results. All of these substances call forth a reaction on the part of the organism very similar to that of injected sulphur, although not as severe. Such results, it is accepted, are to be ascribed to the absorption of foreign proteins. The injection of sulphur, especially in the larger doses, produces a violent local reaction, with necrosis of muscle tissue and an acute inflammatory exudate extending far beyond the point of injection. Of this we have been able to convince ourselves, during the course of our experimental study on animals, which is still in progress. Absorption from the site of injection may then be responsible for the general reaction. In that case the action of sulphur would be analogous to that of non-specific proteins, with increase and mobilization of the leukocytes, which may be accompanied by the mobilization of the proteolytic ferments, as is assumed by Frederick Gay⁹ in explanation of these phenomena. This question however will have to remain open until further studies are made.

Conclusions. 1. The clinical observations and the chemical data of Meyer-Bisch could not be entirely confirmed.

2. Good clinical results were obtained only in arthritis without gross bony obstruction to joint motion.

3. The use of sulphur in the treatment of arthritis gives results very similar to those obtained by the parenteral injections of non-specific proteins, and, until further studies are completed it is doubtful whether sulphur has any specific action in arthritis deformans.

BIBLIOGRAPHY.

1. Bory: *Compt. rend. Soc. de Biol.*, 1907, **63**, 512.
2. Delahaye and Piot: *Compt. rend. Soc. de Biol.*, 1907, **63**, 601.
3. Secor, W. L.: *Med. Rec.*, 1918, **94**, 765.
4. Comrie, J. D.: *Lancet*, 1917, **1**, 991.
5. Meyer-Bisch: *München. med. Wchnschr.*, 1921, **17**, 516; *Ztschr. f. klin. Med.*, 1922, **94**, 237. Meyer-Bisch and Basch, E.: *Biochem. Ztschr.*, 1921, **118**, 39. Meyer-Bisch and Heubner, W.: *Biochem. Ztschr.*, 1921, **122**, 128.
6. Hopkins: *Biochem. Jour.*, 1921, **15**, 286.
7. Haggard: *Jour. Biol. Chem.*, 1921, **49**, 519.
8. Hirsch and Sternberg: *Med. Klin.*, 1923, **19**, 527.
9. Gay, Frederick: *Oxford Med.*, volume I, 247.

SULPHEMOGLOBINEMIA; WITH REPORT OF A CASE HAVING A DEFINITE ETIOLOGY.

BY KARL VOGEL, M.D.,

NEW YORK.

(From the Medical and Pathological Services, St. Luke's Hospital, and the Department of Medicine, Columbia University.)

ALTHOUGH sulphhemoglobinemia is a perfectly definite condition, presenting a clear cut clinical picture and susceptible of exact diagnosis, it is either very rare or cases are seldom recognized. Since its discovery by van den Bergh¹ in 1905, only a score of cases have been reported, and only 3 of the number have been described in this country, the others all occurring in Great Britain or Holland.

On this side of the Atlantic attention was first called to the affection by T. Wood Clarke,² who had observed a case in England and in 1910 established the diagnosis in the person of a young woman who was later brought to St. Luke's Hospital for further investigation. At this time some chemical studies were carried out in the case by the present writer, and in 1916 he was able to demonstrate the same abnormality in another patient, whose history is now given below. In the hope that other instances of the condition would be found, publication of this observation was deferred, but last year Mason and Conroy³ described the second case to be put on record in this country. The writer's case was then briefly reported before the New York Pathological Society,⁴ making it the third put on record here, but since that time some further publications from Holland,⁵ make a somewhat more extensive discussion of the subject seem desirable.

Case Report. On February 28, 1916, a young man, F. R., presented himself for diagnosis. His appearance was remarkable in that his lips and ears were distinctly bluish in color, and his features of a livid pallor. He stated that for the past three weeks he had suffered from vertigo and fainting attacks, a rather severe seizure occurring on the preceding day. He had no headache, no pain, no intestinal nor urinary symptoms; but had been a little shortwinded for two years, which he attributed to cigarette smoking. He was employed in a chemical factory in the production of a photographic developer, para-amido-phenol, made by the electrolysis of nitrobenzene in a concentrated sulphuric acid solution, lead electrodes being used. For the past six weeks he had suffered from itching of the hands, the skin of which had now become thickened, rough and fissured. He had consulted a physician who told him he was suffering from lead poisoning. No drugs had been taken recently except some tablets containing sulphur and cream of tartar which he had been using for some time as treatment for a slight degree of

facial acne. His bowels were regular, and he suffered neither from diarrhea nor constipation.

Examination of his heart and lungs showed no abnormalities and the routine examination of the urine was negative. In the absence of any pulmonary or cardiac lesion to account for the cyanosis, the possibility of poisoning by some of the agents with which his occupation brought him into contact presented itself, notably para-amido-phenol, lead and nitrobenzene. Further tests of the urine proved the absence of phenol, urobilin, urobilinogen, or blood pigments. A blood count gave 5,200,000 red cells per c.mm., hemoglobin, 80 per cent, 10,000 leukocytes with polymorphonuclears, 76 per cent, lymphocytes, 22 per cent, and eosinophiles, 2 per cent. Examination of a smear showed no basophilic stippling of the red cells, nor anything else of note.

On spectroscopical examination of the blood, a band was plainly visible between the C and D lines, that is, about in the position of the characteristic band of methemoglobin, but the possibility of this being an instance of sulphhemoglobinemia suggested itself and further tests were carried out. On comparison of the band in the patient's blood with the spectrum of methemoglobin produced by the action of potassium ferricyanide on a solution of oxyhemoglobin, this band was found to be further to the right than that of methemoglobin. The presence of sulphhemoglobin was confirmed by the addition of a few drops of ammonium sulphide solution to each of the two specimens, when it was found that the band of methemoglobin disappeared, while that in the patient's blood remained unaffected. In order to complete the demonstration of the identity of the pigment, sulphhemoglobin was prepared by passing hydrogen sulphide into a solution of normal blood until a deep violet-red color was produced. The absorption spectrum of this solution was absolutely coincident with that of the patient's blood, and the fluid when treated with ammonium sulphid also gave the characteristic reaction which differentiates sulphhemoglobin from methemoglobin. These observations were carried out with a comparison spectroscope, which makes it possible to note the slightest displacement of the bands.

Further tests were then made on the serum, which was found to contain no sulphhemoglobin, though with Schiff's reagent it showed the presence of a reducing substance, a control test with a normal serum being negative. Tests for nitrites by Olsen's method with sulphanilic acid and d-naphthylamin hydrochlorid were negative in the blood, the serum, and the urine, but positive in the saliva. Repeated tests on the saliva of 9 normal individuals showed that in 3 of these nitrites were present from time to time.

The patient's Wassermann reaction was negative.

He was told to stay away from work and was given cathartics. Two weeks later his appearance had greatly improved, his symptoms

had almost entirely disappeared, and the cyanosis was not very noticeable, but the sulphhemoglobin was still present in marked amount.

On March 22, three weeks after his first visit, he was seen again and reported that he was feeling better and had been at work for the past three days, wearing rubber gloves as he had been directed to do in order to protect his hands from contact with the nitrobenzene. Sulphhemoglobin was still easily recognizable, but was less in amount.

On May 1 he stated that he felt perfectly well, but the sulphhemoglobin band, though fainter, was still unmistakable in a blood dilution of 1 to 3.

May 8. Sulphhemoglobin still present.

June 26. Sulphhemoglobin no longer present in the blood, and the nitrite reaction still present in the saliva, though not as strong as before. The reducing substance in the serum was still present, but much less than before.

September 28. No sulphhemoglobin in the blood, and the saliva negative for nitrites.

In view of the fact that Wallis⁶ ascribed etiological significance to a Gram-negative coccobacillary organism with reducing properties which he found in the saliva of 5 English cases of sulphhemoglobinemia, an attempt was made to confirm this observation, and painstaking bacteriological studies were carried out by the bacteriologist of St. Luke's Hospital, Dr. L. W. Famulener. Cultures from the saliva of the patient were repeatedly made on 5 per cent blood agar, Loeffler's medium, and dextrose broth under both aerobic and anaerobic conditions and at both room and incubator temperatures. Nothing developed in these cultures, however, other than the ordinary types of mouth organisms, and no forms corresponding to the "nitrosobacillus" described by Wallis could be identified. A blood culture made on the usual media under both aerobic and anaerobic conditions gave no growth.

It is well known that cyanosis may be produced by overdoses of a long list of drugs such as acetanilid, phenacetin, trional, sulphonal, potassium chlorate, nitrites, nitrobenzol and di-nitrobenzol. In poisoning by these agents, particularly in the chronic form, there is more or less cyanosis, with headache and prostration, and but few other symptoms, unless the dose has been dangerously large, when coma and death may result. The cyanosis in these cases, which often has been attributed to cardiac depression, is really due to the formation in the blood of methemoglobin, an isomer of oxyhemoglobin which differs from the latter in having its oxygen more firmly bound, so that it is not given up when subjected to a vacuum.

A few cases have been reported, however, by Dutch or British observers in which methemoglobin was present in the blood, but no

external cause for this could be discovered. To this condition the name of enterogenous or idiopathic cyanosis has been given: Stokvis in 1902⁷ reported the first of these cases, and several others have since been described. Talma⁸ found that in these cases the serum was clear, the methemoglobin being contained in the corpuscles only. The patients all suffered from chronic diarrhea, were markedly cyanosed, and as nitrites, which are powerful methemoglobin formers, were found in the blood by van den Bergh and Grutterink,⁹ it has been believed that absorption of nitrites from the intestine was the cause of the disease. In 1 case reported by Gibson and Douglas,¹⁰ the colon bacillus was found in the blood and these authors believed the condition to be of bacterial origin, giving it the designation of microbic cyanosis. Van den Bergh, however, reported 4 other cases, equally of unknown etiology and somewhat resembling the former group, except that the patients all were constipated, and careful study of the blood absorption bands in the spectroscope showed that the band in the red, characteristic of methemoglobin, was a little nearer the yellow than it should be. It was thus discovered that this spectrum was not that of methemoglobin, but that of sulphhemoglobin, an entirely different substance obtainable by treating blood with sulphuretted hydrogen. It was also found that while a temporary disappearance of the methemoglobinemia could be produced by putting the patients on a milk diet for forty-eight hours, no change occurred under like conditions in the sulphhemoglobinemia cases.

Including the present case, 21 well authenticated examples of sulphhemoglobinemia are now on record, 11 from Holland, 7 from England, and 3 from the United States. Of this number only 4 have occurred in males, 2 of van den Bergh's, Mason and Conroy's, and our own; and only 4 of the patients were under twenty-four years of age. In another case in an infant reported by Willémse¹¹ the blood examination is not described in sufficient detail to establish the diagnosis with certainty, and it is therefore not included.

The greenish discoloration of the abdominal parietes sometimes seen in cadavers is known to be due to the postmortem formation of sulphhemoglobin, and it would be a logical assumption to associate the production of sulphhemoglobinemia in the living with the presence of an abnormal increase of sulphuretted hydrogen in the bowel or with the activity of sulphide-forming intestinal bacteria; but clinical observations show that the condition cannot be explained in such a simple manner. It is noteworthy, however, that stagnation of intestinal contents either through chronic constipation or owing to mechanical causes has been a feature in most of the cases of sulphhemoglobinemia reported.

Clarke and Hurtley¹² in a study of the characteristics of sulphhemoglobin were unable to obtain it in crystalline form, but found that it existed in aqueous solution as a definite hemoglobin derivative, and by passing acid-free carbon monoxid gas into such a solution

produced a new substance, carboxy-sulphhemoglobin, with a distinctive spectrum. They also made the important observation that for the production of sulphhemoglobin, conversion of oxyhemoglobin to reduced hemoglobin is an essential preliminary and that powerful reducing agents greatly accelerate the formation of sulphhemoglobin from oxyhemoglobin in the presence of even minute traces of sulphuretted hydrogen. Working along these lines Wallis, who had access to 5 cases in England, endeavored to locate the source of a reducing substance repeatedly demonstrated in the serum of these patients. This substance, capable of producing reduction of the oxyhemoglobin as an essential and primary stage in the formation of sulphhemoglobin, he considered might be of the nature of a hydroxylamin derivative. Its origin he supposed to lie in the activity of a "nitrosobacillus" which he isolated from the saliva of the patients and believed capable of producing the reducing agent needed to form sulphhemoglobin from the sulphuretted hydrogen always present in the body in sufficient quantity in these conditions. It was with the purpose of continuing these observations by Wallis that the bacteriological studies referred to above were made in the case here reported, but with negative results. Failures to find the nitrosobacillus in the saliva are also reported by Long and Spriggs,¹³ and by Mason and Conroy. It is also rather remarkable that an organism which Wallis states could not be made to grow at a temperature above 35°, and which had its optimum temperature of growth and metabolic activity at 25°, should flourish in the human mouth with sufficient vigor to produce nitrites in quantities great enough to be absorbed and give the blood strong reducing properties. Furthermore, Gies¹⁴ and his collaborators have shown that nitrites in varying amounts are more or less constantly to be found in the saliva of healthy persons, as was shown to be the case in our own observations.

In regard to the clinical manifestations of the condition, it may be said that in addition to the cyanosis the most important symptoms are weakness, nervousness, vertigo or fainting attacks, palpitation, headache and constipation. The latter condition has been mentioned in connection with most of the reported cases, though it was not present in Mason and Conroy's case, nor in ours, and may perhaps be nothing more than a coincidence. However, 1 of van den Bergh's patients, a boy of nine years, with a rectal stricture, was cured of his sulphhemoglobinemia as soon as the stenosis of the bowel was relieved, and he reports a similar result in several other cases in which a mechanical obstruction was removed by operation. After a period varying from months to years, during which the symptoms remain mild and more or less indefinite, the blue color of nails, lips, and ears, or of the entire face, develops, and still later more serious disturbances appear. These in some cases have taken the form of definite attacks of exacerbation of the

cyanosis with loss of consciousness, sometimes lasting several hours, during which the patient's condition may be very alarming.

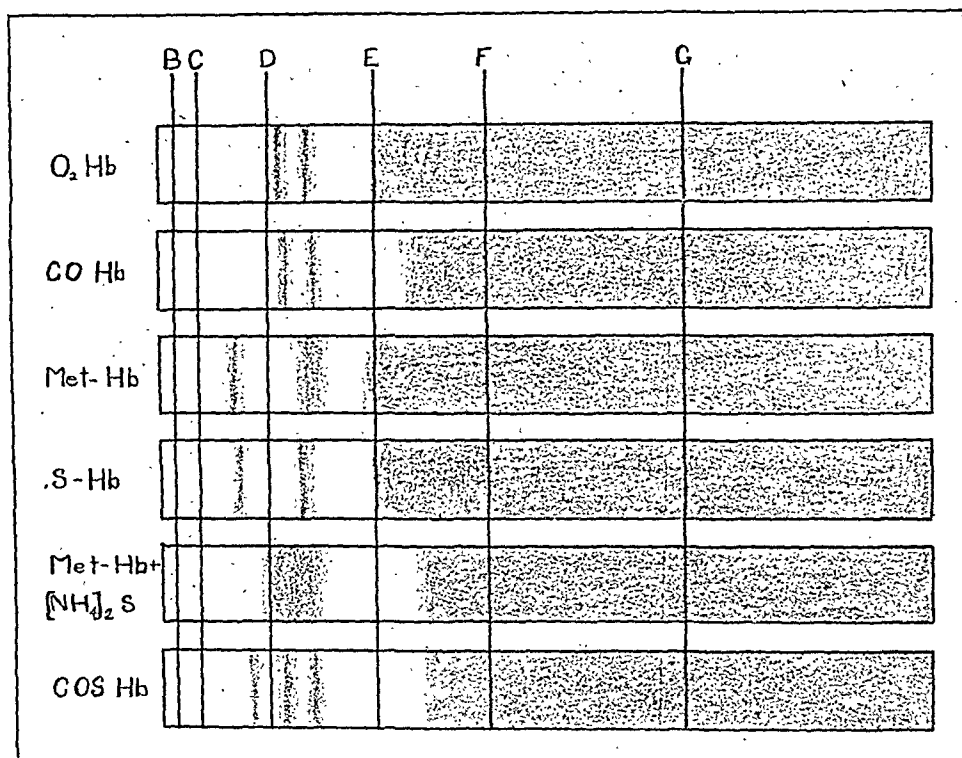
The manner in which the formation of the abnormal blood pigment is brought about is still uncertain and probably differs in different cases. Animals may be killed by the inhalation of hydrogen sulphid without the production of sulphhemoglobin, and evidently two factors must gain access to the blood, sulphuretted hydrogen and a reducing substance. West and Clarke¹⁵ have shown that only exceedingly small amounts of hydrogen sulphid are needed to produce the spectrum of sulphhemoglobin, and apparently the compound is a very stable one, that once formed is not easily broken up. It is possible that the symptoms are in part produced by the anoxemia resulting, for in 1 of van den Bergh's cases from 12.5 per cent to 19 per cent of sulphhemoglobin was found in the blood by gas analysis, showing that a very considerable portion of the hemoglobin had been rendered unfit for its respiratory function.

The earlier efforts to discover the source of the reducing substance needed to activate, as it were, the hydrogen sulphid of the intestine and force the hemoglobin to unite with it have been unsuccessful, but it is believed, as will be shown below, that in the author's case and in 2 others recently described by Snapper an explanation has been found applicable to these particular instances of the affection. The theory of Wallis that a special mouth organism is responsible has lacked confirmation in the cases of Long and Spriggs, Mason and Conroy, and our own, though Wallis believed he obtained good results in treatment by the use of a vaccine prepared from the nitrosobacillus. Long and Spriggs' patient improved after the removal of a carious tooth, and these authors point out that the benefit in one of Wallis' cases may also have been due to the fact that several bad teeth were extracted, but it is of interest that another patient who also improved under the vaccine treatment had had all her teeth removed nine years before the onset of the cyanosis. Free purgation and the removal of all foci of infection would seem to be the most rational modes of treatment. Although the stools of the patients are described as showing nothing abnormal, more careful bacteriological studies than have yet been made would be desirable, and possibly a vaccine from this source might prove of service.

The most important recent contributions to the subject are those of van den Bergh and Engelkes, who describe 5 additional cases and give extensive discussions of the chemistry of sulphhemoglobin. A new test of identity for the substance has been discovered which consists in the fact that the addition of a 1 per cent solution of potassium cyanid causes the spectrum of methemoglobin to change at once to that of cyanhemoglobin, closely resembling that of oxyhemoglobin, but with sulphhemoglobin the change requires twenty-four hours at room temperature. In their experimental work on animals these authors also made an observation of impor-

tance to future investigators, for they found that healthy rabbits apparently sometimes show sulphhemoglobin. Out of 60 animals examined, 12 showed traces of sulphhemoglobin, 7, larger amounts, and 4, considerable quantities, in 1 instance 10.5 per cent in the aortic blood and 12.5 per cent in the portal blood. They also discovered that in certain apparently predisposed human beings the use of sulphur-containing mineral waters may lead to a mild degree of sulphhemoglobinemia.

In addition to the conditions of methemoglobinemia and sulphhemoglobinemia so far referred to in which the observed blood pigment is found only in the corpuscles, a few instances are mentioned in



The absorption spectra of sulphhemoglobin and related hemoglobin derivatives.

the literature in which these substances also appear to have occurred in the serum, apparently always as the result of severe infections with anaërobic bacteria. In an attempt to systematize these various groups van den Bergh suggests that the term "parhemoglobinemia" be adopted for conditions in which the blood spectrum shows a band in the red near the two bands of oxyhemoglobin, and offers the following tentative classification of what he terms the "autotoxic parhemoglobinemias."

1. *Intracorpuseular Methemoglobinemia Without Hemolysis.* In the cases reported always accompanied by longstanding and severe diarrhea, and probably of intestinal origin, with the absorption of nitrites by the blood.

2. *Intracorpuseular Sulphemoglobinemia Without Hemolysis.* Usually but not always associated with intestinal stasis.

3. *Hemolytic Methemoglobinemia.* This group appears to include a few reported cases of anaërobic sepsis and of eclampsia.

4. *Hemolytic Sulphemoglobinemia.* This has occurred in a few instances of anaërobic sepsis.

From a survey of the reported cases of intracorpuseular sulphemoglobinemia it is clear that in some instances there has been definite stagnation of intestinal contents, which would perhaps facilitate the absorption of sulphuretted hydrogen from the bowel, for example, van den Bergh's boy who was cured when his rectal stricture was relieved by operation. There are other cases, however, in which though constipation existed it was not more severe than is constantly being observed without sulphemoglobinemia, and in some patients, for example, Mason and Conroy's and our own, there was no constipation whatever. It is evident that some additional factor in the nature of a reducing substance must be at work to act as an activating agent, and this has been identified in our own case and in 2 lately reported by Snapper. These patients were 2 women in whom there was no question of stagnation in the intestine, since cathartics and enemas were constantly used. The one suffered from a metastasizing carcinoma and the other from tabes, and for the relief of pain 0.5 to 1.5 gm. of phenacetin had been taken daily for a year and for seven months respectively. On stopping the use of the drug the cyanosis and sulphemoglobinemia slowly disappeared, and in the second patient, on resuming the administration of the phenacetin, the sulphemoglobinemia promptly returned. While overdoses of phenacetin may give rise to the formation of methemoglobin, in these cases the doses were too small to produce such a result, and there seems to be no doubt as to the role of the drug in bringing about the necessary conditions for absorption of sulphuretted hydrogen by the red corpuscles. If this is true, it is conceivable in view of the widespread and often habitual use, particularly by women, of coal tar drugs, often in the form of proprietary headache cures, that some of the other reported cases of sulphemoglobinemia may be explained on this basis.

Snapper further states that he gave small doses of phenacetin (0.5 gm.) to dogs over a period of ten days without causing any change in the blood. He then administered precipitated sulphur (1.5 gm.) together with the phenacetin, and sulphemoglobinemia resulted in a day or two, while sulphur given alone produced no effect. This observation has a bearing on the conditions existing in the case of the young man here described. Unlike most of the reported patients, he had not been a sufferer from constipation, and the condition developed in connection with two special circumstances. One was that he had been taking a preparation containing sulphur, and the other that the sulphemoglobinemia developed rather quickly at a time when he was showing the evidences of

nitrobenzene poisoning in the condition of his fissured, scaly and itching hands. After he had been protected from the action of this chemical by absence from his occupation and later by wearing rubber gloves when at work, the sulphhemoglobinemia completely disappeared, a behavior very different from what has generally been noted, as in most cases the affection has proved very intractable to treatment. That over two months elapsed before the blood became free from the abnormal pigment, even though the causative factors were no longer operative, is not remarkable. It has been shown that while sulphuretted hydrogen in the serum is quickly eliminated by the lungs, that bound to the hemoglobin is permanently fixed in this combination. It therefore probably exists during the life of the red cell in which it is contained, and this is now known to be from two to three months. Nitrobenzene alone does not cause sulphhemoglobinemia, and it is suggested that our patient's sulphhemoglobinemia was of a different type from that heretofore described, and that in this case the combination of the two factors of the ingestion of sulphur and the absorption of nitrobenzene brought about the unusual blood condition.

Conclusions: 1. Intracorpuseular sulphhemoglobinemia may be brought about under a variety of conditions.

2. For its production there must be present a reducing substance which serves to make the red cells susceptible to the action of sulphuretted hydrogen derived from the intestine.

3. In some cases this activating substance is of unknown nature and may be of endogenous origin, probably through bacterial action.

4. In some cases the long continued administration of one of the coal tar drugs may furnish the necessary reducing agent.

5. Intestinal stasis favors the production of sulphhemoglobinemia but is not an essential factor.

6. In the case here reported the coincidence of the ingestion of sulphur and absorption of nitrobenzene seems to explain the occurrence of sulphhemoglobinemia in an individual not suffering from intestinal stasis.

REFERENCES.

1. van den Bergh, A. A. H.: *Deutsch. Arch. f. klin. Med.*, 1905, **83**, 86.
2. Clarke, T. W., and Curtis, R. M.: *Med. Rec.*, 1910, **78**, 987.
3. Mason, V. R., and Conroy, F. D.: *Bull. Johns Hopkins Hosp.*, 1921, **32**, 391.
4. Vogel, Karl, and Famulener, L. W.: *Proc. New York Path. Soc.*, 1922, **22**, 163.
5. van den Bergh, A. A. H., and Engelkes, H.: *Nederl. Tijdschr. f. Geneesk.*, 1922, **66**, 2499; *Berl. klin. Wehnschr.*, 1922, **1**, 1930. Snapper, I.: *Nederl. Tijdschr. f. Geneesk.*, 1922, **66**, 2520.
6. Wallis, R. L. M.: *Quart. Jour. Med.*, 1913-1914, **7**, 73.
7. Stokvis, B. J.: *von Leyden's Festschrift*, 1902, **1**, 597.
8. Talma, S.: *Berl. klin. Wehnschr.*, 1902, **39**, 865.
9. van den Bergh, A. A. H., and Grutterink, A.: *Berl. klin. Wehnschr.*, 1906, **43**, 7.
10. Gibson, G. A., and Douglas, C. C.: *Lancet*, 1906, **2**, 72.
11. Willemse, A.: *Nederl. Tijdschr. f. Geneesk.*, 1922, **66**, 445.
12. Clarke, T. W., and Hurtle, W. H.: *Jour. Physiol.*, 1907, **36**, 62.
13. Long, W. C., and Spriggs, E. I.: *Quart. Jour. Med.*, 1917-1918, **11**, 102.
14. Gies and Lathrop: *Jour. Allied Dental Soc.*, 1910, **5**, 262.
15. West and Clarke, T. W.: *Lancet*, 1907, **1**, 272.

THE VALUE OF ALKALI IN DYE THERAPY.

BY VICTOR BURKE, PH.D.,

AND

IRENE GRIEVE, B.S.,

WASHINGTON.

(From the Bacteriology Laboratories, State College of Washington.)

THAT dyes are of value in the treatment of infections has been firmly established. The work of Churchman with gentian-violet, and that of Browning, Graham-Smith, Davis and others with many of the dyes, has determined that the dyes will eventually play a prominent part in the therapy of infected tissues.

Knowledge of the value and limitations of dye therapy is meagre. The experimental work is in the pioneer stage, and much remains to be discovered before the control and use of the dyes can be considered on a sound scientific basis. In general, the experimental work has been designed to establish the practical application and limitations of the dyes in therapy rather than to analyze the factors involved. The active fraction of the molecule of many of the antiseptic dyes is unknown, and there is little knowledge of the factors that affect the value of the dye when applied clinically. The present article represents an attempt to evaluate the effect of the hydrogen-ion concentration on the dye therapy of infected tissues.

It has long been recognized that certain factors influence the action of disinfectants. The *Report of the Committee on Standard Methods of Examining Disinfectants* specifies that the hydrogen-ion concentration, the temperature, the medium surrounding the organisms, the number of organisms, the concentration of the disinfectant and the period of exposure must be taken into consideration in estimating the value of any disinfectant.¹ It follows that these factors should be taken into consideration in developing dye therapy.

Effect of Temperature. Up to the present time little attempt has been made clinically to increase the bacteriostatic action of the dyes. Recently Churchman² has attempted to increase the bacteriostatic action of gentian-violet for *Bacterium coli* by the use of heat, at the same time calling attention to the fact that while it is a common practice to enhance the action of antiseptics by the use of heat this agent has never received much consideration or application in therapy. That the application of heat in dye therapy has serious limitations is recognized by Churchman, but he believes that the application of hot dye will be more effective than a similar application of cold dye. Churchman's experiments

show that gentian-violet at 50° C. destroys *Bacterium coli* in one hour, while at 35° C. it has no appreciable effect in one and a half hours.

Effect of Hydrogen-ion Concentration. The effect of the reaction of the secretions to be sterilized by the dye deserves special consideration. The control of the reaction is not subject to the same limitations as the control of heat, although extremes in acidity or alkalinity are injurious to the tissues. The tissues have greater tolerance for alkali than for acid. It is not advisable to acidify the body fluids or secretions, except to a slight extent in special fluids, like the urine, in order to increase the antiseptic power of a disinfectant. On the other hand, it is quite practical greatly to increase the alkalinity of body fluids and secretions by the administration of sodium bicarbonate, without danger of injury to the tissues. If the action of the dyes for bacteria can be increased by an increase in the alkalinity of the fluids and secretions to be disinfected, then we have at our disposal a satisfactory means of increasing the value of the dyes.

There is considerable evidence to prove that an increase in alkalinity increases the action of many of the dyes for bacteria. It remains to be determined whether an increase in bactericidal action for one species of bacteria is accompanied by an increase in bactericidal action for all bacteria. It is quite conceivable that while we are increasing the bactericidal action of a disinfectant for one species we may be reducing it, or at least not altering it, for another species. Davis³ states that acriflavin inhibits staphylococcus and *Bacterium coli* in alkaline urine (pH 8.0) in a dilution of 1 to 100,000, while in an acid urine (pH 6.0) it is almost equally effective for staphylococcus, but loses most of its action for *Bacterium coli*.

There is also evidence to show that an increase in alkalinity decreases the bactericidal action of at least one dye, acid fuchsin and other disinfectants, such as mercuric chloride.

Graham-Smith,⁴ in determining what factors influence the action of dyes and allied compounds on bacteria, demonstrated that alkalinity increased the bacteriostatic action of homoflavin and crystal-violet and decreased the action of quinone for bacteria. He concludes that the most beneficial results are likely to be obtained if the wounds are first thoroughly cleaned and the dye solution is made in a reaction at which the compound acts most effectively, provided such a reaction is not harmful to tissue. The effect of the alkali was more marked in agar than in meat extract or ox serum.

Davis and White⁵ and later Davis⁶ have shown that acriflavin and proflavin are more active in alkaline urine. Davis states that acriflavin inhibits staphylococcus and *Bacterium coli* in an alkaline urine (pH 8.0) in a dilution of 1 to 100,000. In an acid urine (pH 6.0)

it is almost equally efficient for staphylococcus but loses most of its action on *Bacterium coli*, a dilution between 1 to 5000 and 1 to 7500 being necessary to destroy the latter organisms. This seems to indicate that an increase in alkalinity of the urine from pH 6.0 to pH 8.0 has little effect on the antiseptic power of this dye for staphylococcus but greatly increases its action for *Bacterium coli*.

Browning, Gulbranson and Kennaway⁷ have shown that the antiseptic action of the acridin compounds for *Bacterium coli* is increased in urine and peptone water with an increase in alkalinity. This action is reversed with mercuric chloride. The authors state that the antiseptic action for staphylococcus is also increased, but not to the same degree. The effect is similar whether the reaction is adjusted with hydrochloric acid, sodium hydroxide or alkaline phosphate.

Beckwith⁸ has shown that an increase in alkalinity increases the action of crystal-violet in bile and saline, acriflavin in serum, brilliant green and basic fuchsin in bile, for *Bacterium typhosum*, and that the effect on acid fuchsin is the reverse.

Kligler⁹ concludes that the reaction of the medium modifies the antiseptic action of the dyes, that the germicidal action is a function of the benzene nucleus, that the number of alkyl radicals increases the antiseptic power and that this is increased to a greater extent by an ethyl than a methyl group.

Burke¹⁰ has shown that a solution of sodium bicarbonate improves the intensity or concentration of the dyes, gentian-violet, methyl-violet and crystal-violet, remaining in the Gram-positive organisms when stained by the Gram method. Lactic acid produced the opposite results. The suggestion is made that these facts indicate the possibility of improving dye therapy by the addition of an alkali.

The work of Burke led the authors of this paper to undertake a more intensive study of the effect of alkali in dye therapy. The present paper contains a preliminary report in order to draw the attention of clinicians using dye therapy to the possibility of enhancing the value of the treatment by controlling the hydrogen-ion concentration. There is sufficient evidence to warrant the clinical application of alkali in the treatment of infected surfaces with dyes, such as gentian-violet, crystal-violet, acriflavin, homo-flavin, proflavin, basic fuchsin and brilliant green. Since the effect of alkali on the antiseptic action of many dyes has not been determined, and since the antiseptic action of some of the dyes is reduced, an indiscriminate use of alkali is not recommended.

Experimental. *Experiment 1.* To determine the effect of an increase in alkalinity on the bactericidal action of gentian-violet on a Gram-negative organism, *Bacterium coli*.

Technic: Samples of Dunham's peptone broth were adjusted

with sodium carbonate to the pH value of 6.6, 7.0, 7.4, 7.8, 8.2 and 8.6. Five cubic centimeters of each sample of broth were placed in test-tubes. A sufficient amount of a 1 to 200 aqueous solution of

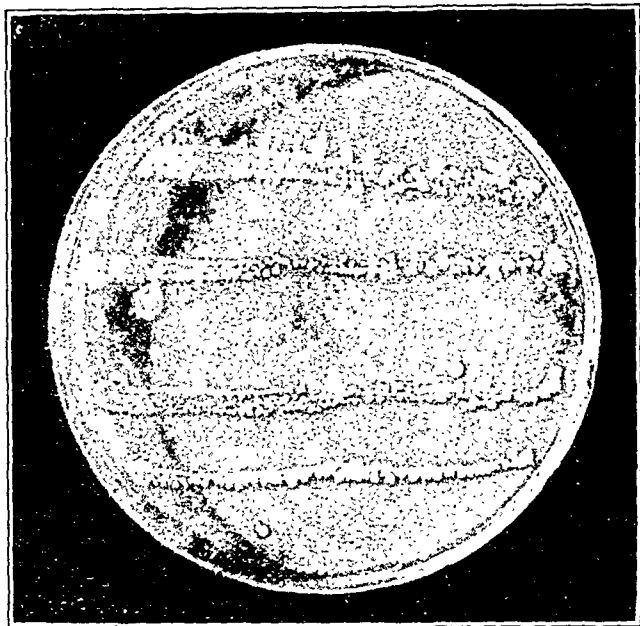


FIG. 1.—Strokes of *Bacterium coli* after exposure to a 1 to 1000 dilution of gentian-violet in broth having a pH 6 for one-half, one, two and three and one-half hour periods.

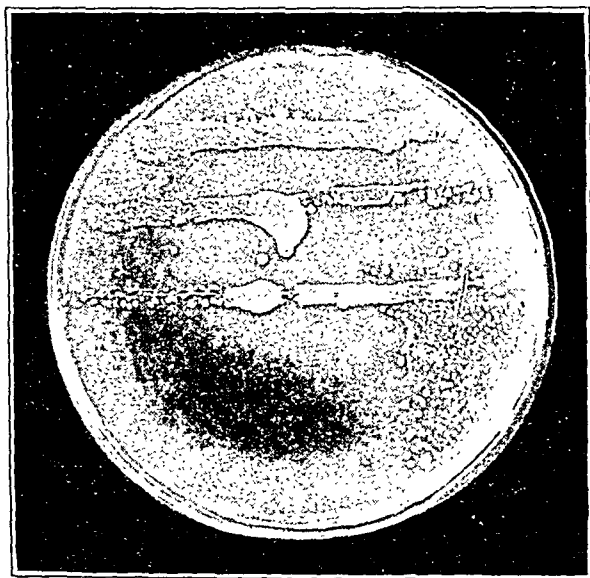
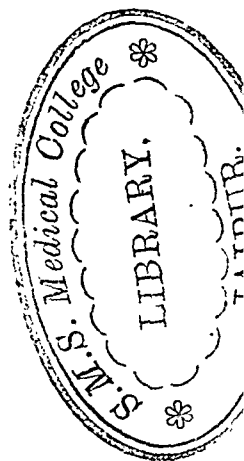


FIG. 2.—Strokes of *Bacterium coli* after exposure to a 1 to 1000 dilution of gentian-violet in broth having a pH 7.8 for one-half, one, two and three and one half hour periods.

gentian-violet was added to each tube to make a dilution of 1 to 1000 and also a 0.1 cc of a twenty-four hour neutral peptone broth culture of *Bacterium coli*. The tubes were incubated at 37° C. At inter-



vals up to three and a half hours loopfuls were taken from each tube and streaked on neutral agar. The results obtained are given in Table I, and indicate a decided increase in bactericidal action of

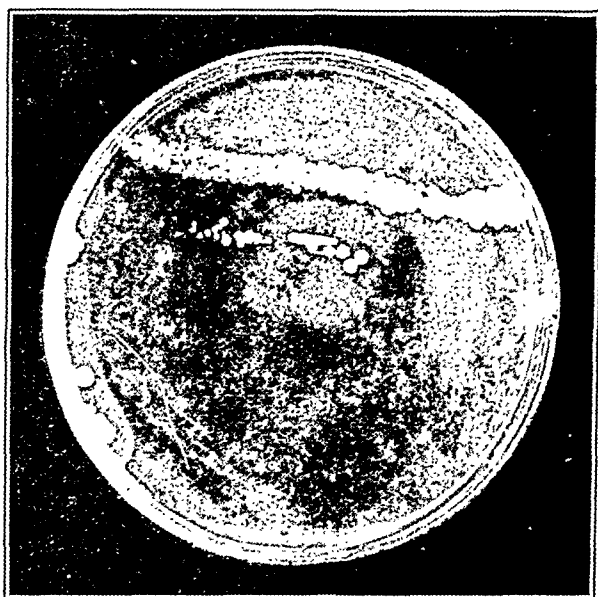


FIG. 3.—Strokes of *Bacterium coli* after exposure to a 1 to 1000 dilution of gentian-violet in broth having a pH 8.2 for one-half, one, two and three and one-half hour periods.

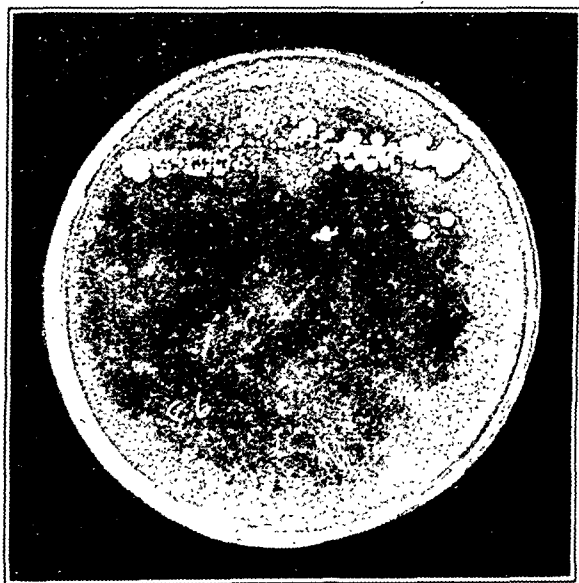


FIG. 4.—Strokes of *Bacterium coli* after exposure to a 1 to 1000 dilution of gentian-violet in broth having a pH 8.6 for one-half, one, two and three and one-half hour periods.

the dye with an increase in alkalinity. The more alkaline the broth the more rapidly the organisms were destroyed. Figs. 1, 2, 3 and 4 are of some of the plates obtained in this experiment.

The controls, made from organisms exposed to a pH 6.6 and 8.6, resembled Fig. 1. Figs. 3 and 4 indicate an individual variation of *Bacterium coli* in resistance to the dye. In the second streaks on Figs. 3 and 4 only a few organisms survived. Comparable results were obtained by plating out and counting the number of viable organisms per 1 cc remaining after each period of exposure. Part of the decrease in numbers may have been due to the increased alkalinity rather than to the dye since a pH 8.6 approaches the maximum range for the multiplication of *Bacterium coli*.

In a similar experiment comparable results were obtained with the Gram-positive organism, *Staphylococcus aureus*.

TABLE I.—EXPERIMENT 1: THE EFFECT OF AN INCREASE IN ALKALINITY ON THE BACTERICIDAL ACTION OF GENTIAN-VIOLET FOR BACTERIUM COLI.

Reaction.	Period of exposure in hours.			
	$\frac{1}{2}$	1	2	3 $\frac{1}{2}$
pH 6.6	+	+	+	+
7.0	+	+	+	+
7.4	+	+	+	One colony
7.8	+	+	M. R.	—
8.2	+	M. R.	—	—
8.6	+	Less	—	—
Controls	+	+	+	+

+ indicates viable organisms. M. R. indicates marked reduction in the number of colonies.

TABLE II.—EXPERIMENT 2: THE EFFECT OF AN INCREASE IN ALKALINITY ON THE BACTERIOSTATIC ACTION OF GENTIAN-VIOLET FOR A GRAM-NEGATIVE ORGANISM, BACTERIUM COLI.

Reaction.	Dilution of dye.					
	1:2000	1:4000	1:5000	1:8000	1:10,000	1:20,000.
pH 6.6	—	—	—	—	—	+
7.0	—	—	—	—	—	+
7.4	—	—	—	—	—	—
8.0	—	—	—	—	—	—
8.2	—	—	—	—	—	—
8.6	—	—	—	—	—	—
Control	+	+	+	+	+	+

+ indicates presence of gas.

Experiment 2. To determine the effect of an increase in alkalinity on the bacteriostatic action of gentian-violet on a Gram-negative organism, *Bacterium coli*.

Technic: Samples of nutrient broth containing 1 per cent lactose were adjusted with sodium bicarbonate to the pH values of 6.6, 7.0, 7.4, 8.0, 8.2 and 8.6. Portions of each sample of broth were placed in seven fermentation tubes. Sufficient volumes of a 1 to 200 dilution of gentian-violet were added to the tubes to make dilutions of 1 to 2000, 1 to 4000, 1 to 5000, 1 to 8000, 1 to 10,000 and 1 to 20,000. To each tube was added 0.1 cc of a twenty-four-hour culture of *Bacterium coli* grown on neutral peptone

broth. The tubes were incubated twenty-four hours and the results read. The presence of gas served as an index to growth. The results obtained are given in Table II, and indicate that with an increase in alkalinity there is an increase in the bacteriostatic as well as bactericidal action of gentian-violet for *Bacterium coli*.

Experiment 3. To determine the effect of lactic acid on the bactericidal action of gentian-violet for *Staphylococcus aureus*.

Technic: Nutrient broth was titrated to pH 7.8 with sodium bicarbonate. Portions of this were titrated to pH 7.0 and pH 6.2 with lactic acid; 5-cc volumes of the three samples were placed in three test-tubes. To each tube was added 0.1 cc of a twenty-four-hour neutral broth culture of *Staphylococcus aureus* and sufficient gentian-violet solution to make a 1 to 10,000 dilution of the dye. Transplants by the loop method were made from each tube to agar plates at one-half, one and two-hour intervals. The plates were incubated twenty-four hours. The results obtained demonstrate that lactic acid reduces the bactericidal action of gentian-violet for *Staphylococcus aureus*. The streaks on the agar plates from the more acid tubes either failed to show growth or the number of colonies appearing was greatly reduced.

Pus frequently contains lactic acid. Dyes are reported as less effective in the late stages of infection when many organisms are present. This reduction in effectiveness may be due, in part at least, to lactic acid.

The controls in this and the other experiments demonstrated that the inhibition or death of the cells was not due to the hydrogen-ion concentration alone but to the hydrogen-ion concentration in association with the dye.

A review of the literature and of the foregoing experiments indicates that an increase in the alkalinity of the medium surrounding the organisms increases the bactericidal action of many dyes, the most important ones being crystal-violet, methyl-violet, gentian-violet, basic fuchsin, homoflavin, acriflavin, proflavin and brilliant green, for both Gram-positive and Gram-negative bacteria. It does not increase the bactericidal action of all dyes or disinfectants. The action of acid fuchsin and mercuric chloride is decreased by the addition of alkali. The fact that an increase in alkalinity increases the bactericidal action of a dye on one species of bacteria does not prove that it will increase the action on all species. However, there is no evidence to show that alkali will increase the action of a dye on one species and decrease it on another. Therefore if alkali increases the action of a dye on one species it is advisable to apply it with the given dye in the treatment of infection with other organisms. The alkali used seems to be immaterial. Sodium hydroxide, alkaline phosphate, sodium carbonate and sodium bicarbonate have been shown to increase the action of the dyes.

How Dyes Act as Disinfectants. There is some evidence to show that the bactericidal action of dyes depends upon the molecular structure, particularly the benzene nucleus. Generally the greater the number of alkali radicals the greater the toxicity of the dye. Basic dyes are in general more toxic than acid dyes. The antiseptic power is enhanced to a greater extent by an ethyl than a methyl group. The relative position of the group may be important. In the triphenylmethane dyes the bactericidal power apparently follows the double bond.¹¹

It is not known how the dyes cause the death of cells or how alkali increases this action. The alkali may alter either the cell or the dye. Kligler has suggested that the effect of a change in the reaction is probably due to an alteration of the cell. The effect of the dye does not depend upon penetration, but may vary with the concentration within the cell. Burke has shown that alkali increases the amount of the dye remaining in Gram-positive organisms in the Gram-staining. Whether this result is due to a change in the cell wall, or a greater concentration of the dye within the cells, or to a change in the size of the molecules of the dye-iodin precipitate was not determined. If alkali increases the concentration of the dye within the cells this may possibly account for the increased bactericidal action. According to Langer,¹² a disinfectant is effective in proportion to the degree that it is taken up within the bacterial cell. Also the effectiveness depends upon the solution state. With increased aggregation and reduced diffusivity there is an increased disinfecting power. Alkali reduces the diffusion of a dye, and this may account for its effect on the bactericidal action.

The difference in degree of absorption by the cells may account for the difference in resistance between the Gram-negative and Gram-positive bacteria. *Bacterium coli* exposed to a 1 to 1000 dilution of dye may not absorb more dye than *Staphylococcus aureus* exposed to a 1 to 50,000 dilution. The organisms in each group, Gram-positive and Gram-negative, vary greatly in resistance to the dyes.

Effect of Hydrogen-ion Concentration on Bacteria. In estimating the value of alkali in dye therapy we must consider the effect of alkali on the various factors of infection and resistance. Our knowledge of the effect of the reaction on these factors is decidedly limited, but there is much to favor the view that alkali will prove to be beneficial in the treatment of infections for other reasons than for its effect on the antiseptic power of the dyes.

In reviewing the effect of the hydrogen-ion concentration on the growth of bacteria in the tissues and their power to produce disease we find much of interest. For each species of bacteria there is a minimum, optimum and maximum hydrogen-ion concentration for growth and for life. As soon as the reaction varies beyond the

minimum or maximum there is reduction in growth or loss of life. The optimum reaction for the most rapid multiplication of many of the pathogenic organisms is unknown. The range for growth has, in many cases, been reported. But the reaction which begins to check the rate of growth has not been determined for many of the pathogens. Before we can determine the possibility of checking bacterial action on the tissues by altering the reaction we must first determine the optimum and maximum reaction for multiplication and toxin production. *Corynebacterium diphtheriæ* will multiply rapidly in a reaction in which it will not produce toxin. This suggests that the reaction of the body fluids may in some cases determine the carrier state.

Recently Cohen¹³ and Cohen and Clark¹⁴ have shown that the optimum hydrogen-ion concentration for life may differ from that for growth. A change in reaction beyond the optimum has a decided effect upon both growth and life of *Bacterium coli* and *Bacterium typhosum*. The death-rate of *Bacterium typhosum* is at a minimum in dilute buffer solutions in the zone between pH 5.0 and pH 6.4. The pH zone for optimum growth lies between 6.2 and 7.2. It is important to note that the optimum for life (lowest death-rate) differs from the optimum for growth (most rapid multiplication). If the organisms are not multiplying they are likely to produce less serious pathological conditions in the host. It is obvious that under certain conditions in the treatment of infections our object may be attained as effectively if we aim to prevent growth as if we aim to cause death of the invading organism. If we can reduce the rate of multiplication by altering the reaction to either acid or alkaline, away from the optimum if not to the maximum, we gain something, provided such a change in reaction comes within the range of tolerance of the tissues. It remains to be determined whether a system of treatment based upon these facts can be developed. Under what conditions it is possible or advisable to alter tissue reactions in order to check bacterial activity remains to be determined.

Henderson and Palmer¹⁵ have shown that it is possible by the administration of sodium bicarbonate by mouth to cause the urine to have a reaction of pH 8.7. This is beyond the optimum for the growth of *Bacterium coli* and should increase the lag, and check but not prevent the growth of the organism. The greatest acidity found in urine was pH 4.7. A change from pH 4.7 to pH 8.7 will greatly affect the antiseptic power of the dyes. The urine is normally acid and, although bladder infections with proteolytic organisms may occasionally cause it to become alkaline, it would seem advisable to administer sodium bicarbonate whenever utilizing dye therapy in the treatment of the bladder or ureter.

The hydrogen-ion concentration in some infections is antagonistic to the invading organism. The exudate in the pneumonic lung is

usually acid with a hydrogen-ion concentration of pH 6.0 or more. The pneumococcus organisms are very sensitive to acid and die in a few hours when exposed to a reaction of pH 6.0. Thus, the reaction in disease may be favorable to the host and a return to neutrality or alkalinity favorable to the invading organism in so far as the single factor of growth is concerned. However, since other factors in infection and resistance are of considerable importance it is necessary in cases of this kind to take them into consideration before reaching a decision as to the advisability of changing the hydrogen-ion concentration. Also if we were adding a disinfectant, such as a dye at the time of making the reaction more alkaline we can ignore the direct effect of the changed reaction on the organisms and depend upon the dye. It is obvious that the alkali dye combination will be more effective against those organisms which are affected by the hydrogen-ion concentration used; in other words, in those cases in which the alkali checks the organisms as well as increases the antiseptic power of the dye. For this reason the limits of tissue tolerance for alkali should be reached.

Bacterial toxins, enzymes, acids and gases are important factors in disease. Their production by bacteria and their action after production is influenced by the hydrogen-ion concentration. Bacterial proteolytic enzymes act best in an alkaline medium. The optimum reaction for diphtheria toxin production lies between pH 7.2 and pH 8.0. Under other conditions there may be abundant growth but no toxin production. Diphtheria toxin is more sensitive to acid than to alkali. Botulinus toxin is not affected by acid. The peptolytic enzymes of the hemolytic streptococci are most active at pH 7.0, their action decreasing as the reaction varies to either the acid or alkaline side.¹⁶ Proteolysis in the pneumonic lung, an important factor in recovery, is unquestionably influenced by the hydrogen-ion concentration of the exudate. These few illustrations suffice to indicate how the hydrogen-ion concentration may influence the course of an infection by affecting the growth, rate of multiplication, toxin production and enzyme action. Whether altering the hydrogen-ion concentration can be effectively utilized in the treatment of many infectious diseases remains to be determined. This will be determined partly by the difficulty of control and partly by the effect on the defensive mechanism of the body.

Effect of Hydrogen-ion Concentration on Resistance. The factors in host resistance and repair, such as complement, phagocytes and their enzymes, and fibroblast formation, are affected by changes in the hydrogen-ion concentration. Very dilute acid favors the action of most but not all ferments, and alkali is unfavorable to many of them. The action of the complement is affected by both acid and alkali. This is also true of the agglutinins antitoxin and

the amboceptor. Infectious acidosis is an important factor in recovery. In acidosis resulting from infectious diseases, such as cholera, the alkali treatment has proven beneficial. According to Sherwood, carbon dioxide, lactic acid and acetone may be present in the blood during disease in sufficient amount to favor infection or interfere with recovery.

There is evidence to show that phagocytosis and phagocytic proteolysis are affected by the hydrogen-ion concentration. Opsonins are sensitive to changes in reaction. Phagocytes and their enzymes are believed to be more effective in an alkaline than an acid medium. The intracellular proteoses of the polymorphonuclear leukocytes are more active in an alkaline medium. These leukocytes have two enzymes: One active in an acid medium, with an optimum of pH 3.5; the other active in an alkaline medium, with an optimum of pH 7.8. Both are active between pH 6.0 and 7.0. Leukocytes are said to be negatively chemotactic to lactic acid in all concentrations. They are weakly positively chemotactic to dilute sodium and potassium salts. Calcium salts increase phagocytosis.

The hydrogen-ion concentration is a dominant factor in the liquefaction and absorption of dead tissues. A septic infarct liquifies more rapidly than an aseptic infarct, due to the greater number of leukocytes in the former. Infarcts of small size are digested by the leukocytic enzymes more rapidly than large infarcts because the former are kept alkaline by blood seepage. Resolution in the pneumonic lung is due partly to leukocytic enzymes, that is, heterolysis, and partly to autolytic enzymes. Autolysis is more rapid in gray hepatization than in red hepatization, due to the absence of anti-enzymes and increase in acidity in the former. Heterolysis is more rapid in red hepatization, due to the more alkaline reaction. As indicated by these facts, the proteolytic enzymes of the polymorphonuclear leukocytes are more active in an alkaline medium and the enzymes of the tissue cells and mononuclear leukocytes more active in an acid medium. The maximum cellular autolysis of several of the tissues takes place in a pH 5.0 to 6.0. A small excess of acid inhibits the heterolysis, due to leukocytic enzymes. The reaction of the blood reduces cellular autolysis to a minimum but favors heterolysis. In autolytic organs fatty acids and lactic acid are usually present. Autolysis of cells does not begin until normal alkalinity is reduced. Autolysis can be controlled by controlling the hydrogen-ion concentration. Maximum liquefaction depends on initial acidity followed by a slight alkalinity. Since the products of protein liquefaction are toxic, it may be advisable to develop control of the rate of autolysis and heterolysis of dead tissues and exudates.

The effect of autolytic products on the invading organism is uncertain. Autolytic products are thought to inhibit bacteria, but

to what degree we are unaware. They may account for sterile pus and neutralize toxins. The autolysate of fibrin is bactericidal to staphylococcus. A rapid lysis of bacterial cells may increase the liberation of endotoxins to such an extent as to be detrimental rather than beneficial.

The hydrogen-ion concentration in the pneumonic lung is an important factor in the death of the pneumococci and in resolution. The pneumonic lung may have a reaction of pH 5.4, a hydrogen-ion concentration in which the pneumococci will live but a short time. Resolution frequently follows gray hepatization. In such cases, in which the exudate is extremely acid, the liquefaction of the exudate must be brought about largely by enzymes other than those from the polymorphonuclear leukocytes which are inhibited by acid. Thus, the acidity reduces the leukocytic action, but at the same time reduces the necessity for it by destroying the pneumococci. Too rapid proteolysis in the pneumonic lung may be detrimental. The toxic effects in pneumonia are due partly, at least, to protein cleavage rather than to bacterial secretions. Sterile suppuration has the same effect on metabolism as septic pus, due to protein cleavage. It is evident that any effort to determine the hydrogen-ion concentration of the pneumonic lung most favorable for recovery must take into consideration the effect of the reaction on the invading organism, coccus or bacillus, the effect on leukocytic action and the effect on resolution. This affords a problem worthy of intensive investigation.

The effect of a change in the hydrogen-ion concentration on the bactericidal action of some of the body fluids is known. Browning, Gulbranson and Kennaway state that alkaline phosphate added to serum *in vitro* does not affect its bactericidal action. The resistance of rabbits to anthrax infection is increased by treating the rabbits with alkali. This is not due to increased alkalinity of the blood serum (Cushny¹⁷). The antiseptic power of rabbit bile is increased by feeding the animals alkali.¹⁸ Beckwith doubts the possibility of curing the typhoid carrier state by the use of alkali.¹⁹ Urine *in vivo* can be made sufficiently alkaline to check but not inhibit the rate of multiplication of *Bacterium coli* and *Bacterium typhosum*.

Hydrogen-ion concentration is an important factor in wound healing. The healing of aseptic wounds, by first intention, requires mainly the absorption of injured cells and fibroblast formation. The secretions of aseptic wounds are alkaline. Under such conditions fibroblast formation takes place rapidly. In septic wounds the pus serum may be alkaline or acid, depending upon the organism present; pus serum usually contains lactic acid. Edema fluids are alkaline, except when bacterial activity leads to acid production. Edema, due to acid, is reduced by the blood alkali. Inflammatory exudates frequently have a hydrogen-ion concentration of pH 6.0 or more. Acid in leukocytic exudates retards leukocytic

digestion of dead tissue and bacterial cells and checks healing. It favors autolysis of dead tissue. It retards fibroblast formation and reduces the action of many disinfectants. Hyperemia is sometimes desirable in wound healing, and in these cases the treatment should be designed to bring it about if the infection does not. The autolysate of dead tissue is toxic. Dead tissue is removed by operation whenever possible and in such cases ceases to be a factor. In fresh clean wounds fibroblast formation is most important, and this is favored by an alkaline secretion. Dilute alkalies, such as some of the potassium salts, stimulate cell growth. An excess of H or OH ions leads to cell death. Mechanical injury to a cell usually results in increased acidity. A return to normal alkalinity is essential to life.

From the above discussion it is evident that the hydrogen-ion concentration has an important bearing on body resistance and repair as well as on bacterial activity or infection. Analysis shows that we are dealing with an exceedingly complex question. Whether or not in disease the reaction should be kept most favorable for the host or least favorable for the invading organism remains to be determined. In some types of infection the most favorable reaction for the host will be the least favorable for the invading organism. In other cases the reverse of this will be true. In some types of infection it might be advisable to favor the host regardless of the effect on the bacteria, and in other cases to destroy the bacteria regardless of the effect on the host. Some of the immune factors that are influenced by the reaction are more important than others. Experimentation alone will determine under what conditions it is advisable to change the hydrogen-ion concentration. This is a field of investigation in which much remains to be done. In the present article we can simply call attention to its possibilities and importance.

Effect of Hydrogen-ion Concentration on the Toxicity of Dyes for Body Cells. We have shown that alkali increases the bactericidal action of many dyes. It also favors the action of the leukocytes. It is important to know whether the increase in bactericidal action of the dye is accompanied by an increase in toxicity for body cells and to the same extent. If the bacteriotropic action of the dye is increased more rapidly than the leukocytotropic action then we gain much by the use of alkali. If the action against the bacteria and the leukocytes increases at the same rate this may necessitate a change in the dilutions used in dye therapy.

Investigators are not in agreement as to whether dyes are more toxic or less toxic for body cells than for bacteria. This is important, since if dyes are more toxic for body cells than for bacteria we must consider the phagocytes eliminated as a factor in healing during the application of the dye. Infection indicates a leukocytic failure to repel the invading organism. It has been claimed that

the main function of a disinfectant is to stimulate the body defenses. It is obvious that this cannot always be true. Weak alkalis favor leukocytic action. Whether or not this will enable the leukocytes to resist greater concentrations of the dyes remains to be determined. Dyes tend to reduce the action of the phagocytes but not to inhibit it entirely in dilutions that are bactericidal for many bacteria, principally the Gram-positive organisms. The lethal concentration of most of the dyes for *Bacterium coli* in serum inhibits phagocytosis.²⁰ This statement will probably be found to hold true for *Bacterium coli* in acid pus and infectious exudates. Whether it still holds true after such pus and exudates are made alkaline is unknown.

The question is complex, and experimentation alone will produce a satisfactory answer. And regardless of the comparative effect on bacteriotropism and leukocytotropism we must consider the effect of alkalization on the defensive mechanism as a whole before we can scientifically estimate the value of the alkali treatment. We believe that the ultimate fate of the dyes as chemotherapeutic agents in infection is dependent largely upon the effect and control of the hydrogen-ion concentration. More experimental evidence of the effect of dyes on body cells under tissue culture conditions and in the animal body is needed.

Methods of Application. There is evidence to show that alkali increases the bactericidal action of the dye whether alkalization is brought about before or after the dye is added to the medium containing the bacteria. Davis has shown that the action of the dye is greater in alkaline than in acid urine. A number of investigators have reported an increase in bactericidal action, with an increase in alkalinity of broth. Presumably the reaction of the media was adjusted before the organism and dye were added. This is true in our own experiments. It has not been determined that the increase in the action is as great when the alkali is added to the dye before application. Burke has shown that the staining of Gram-positive organisms is intensified by the addition of alkali whether this is added to the organisms or to the dye before application. It seems probable that the alkali is as effective in increasing the bactericidal action of the dye whether added to the organism or to the dye just before application. However, since alkali added to the dye causes a return to the leukobase in a few hours, it seems advisable to add the alkali to the tissues before or after the dye rather than to the dye.

Body fluids can be made alkaline by the administration of sodium bicarbonate. The administration of 4 to 12 gm. of sodium bicarbonate per os will cause the urine to develop a hydrogen-ion concentration of pH 8.7 in a few hours. Two to 4 gm. three times a day keeps the urine alkaline. Urine may have a reaction of pH 4.7. A change to pH 8.7 will greatly increase the bactericidal action of

many dyes and also reduce the rate of multiplication of certain bacteria, such as *Bacterium coli*. The nearer the reaction comes to the limits of tissue tolerance the less favorable become conditions for growth.²¹ Alkalinization of the urine should always precede the treatment of bladder and urethral infections with dyes. Davis was successful in producing antiseptic urine by the administration of sodium bicarbonate and proflavin. Whether sodium bicarbonate per os will prove effective in changing the reaction of empyema fluids and pus serum is unknown to us. If not, then an alkaline wash is indicated.

Whenever feasible infected surfaces should be cleaned of pus, blood and mucus with a good cleansing agent, such as hydrogen peroxide and then washed thoroughly with an alkaline wash. Hydrogen peroxide is slightly acid and should be neutralized with a little sodium bicarbonate before use. A slightly alkaline soap will be found beneficial in cleansing wounds, and appears to have a beneficial effect when applied to dressings. It has a tendency, however, to cause swelling of epithelial cells, and thus reduce penetration of disinfectants.

The kind and strength of alkaline wash to be used on infected surfaces should vary with the surface to be treated and possibly with the stage of healing. The more alkaline the wash the stronger the bactericidal action of the dye, but in general corrosive washes should be avoided. In the treatment of skin infections a fairly strong solution of sodium bicarbonate solution may be used. In the direct application of alkaline washes to mucus surfaces more attention should be paid to the composition and hydrogen-ion concentration of the wash. A combination of salts that are positively chemotactic to leukocytes, non-irritating and stimulating to enzymes and fibroblast formation or granulation tissue is to be recommended. Calcium ions are positively chemotactic to leukocytes. This is also true of diacidic sodium phosphate. Calcium and magnesium salts increase phagocytosis. Locke's solution is slightly alkaline, stimulating cell proliferation, and should prove to be a satisfactory wash for sensitive surfaces.

The frequency of application of the dye will be affected by the use of alkali. Alkali causes a return of the dye to a leukobase in a few hours to several days, depending upon the strength of alkali used. The leukobase of a dye is less bactericidal and less toxic than the dye.

Dangers of Dye Therapy and Alkalinization. There seems to be little or no danger attendant upon the local application of dyes. In strong concentration they are slightly irritating to mucous surfaces. When applied to fresh or infected wounds there is no irritation felt by the patient. Compared with other disinfectants of equal bactericidal action the dyes are less likely to prove objectionable to the patient. Davis and others have shown that many

of the dyes are toxic when injected intravenously. Most of those that are not toxic are ineffective. At the present time the intravenous injection of dyes should be practised with caution. Not more than 5 mg. per kilo of body weight should be injected intravenously. The solution should be made up fresh in normal saline prepared from freshly distilled slightly alkaline water. Davis reports that large doses of acriflavin and proflavin *per os* when administered to rabbits are toxic but that small doses were administered over a long period without injurious effect. He reports patients complaining of nausea following a dose of 0.3 gm. but not after 0.1 gm. Uhlenhuth and Messerschmidt report methyl-violet and fuchsin as being somewhat toxic and causing necrosis at the site of injection.²² Dyes in low concentration stimulate cell growth and may account for the development of bladder tumors. Years of contact seems to be necessary for tumor development, since none has been reported following an exposure of less than ten years. Scarlet red has been used to stimulate epithelial growth over granulation tissue.

The improper use of dyes may be detrimental to the host by stimulating bacterial activity or reducing the resistance of the host. Neufeld, Schiemann and Baumgarten²³ record that subtherapeutic doses appear to accelerate the infection. Also many of their animals died from dye poisoning. Dye therapy is in the experimental stage and, while clinical application is desirable, dye therapy should be used with caution, particularly in combination with alkali therapy.

When used in great concentration some of the dyes may check healing. Mueller²⁴ states that under tissue culture conditions the triphenylmethane dyes inhibit tissue cells in dilutions not inhibiting streptococci. With the flavins the inhibiting dilution is the same for tissue cells and streptococci. Mueller points out that this may not be true in the body, since the conditions would be more favorable for the tissue cells and less favorable for the organisms. Russel records gentian-violet as inhibiting the growth of certain tissue cells and not others under tissue culture conditions.²⁵ The proper use of an alkaline wash will make conditions more favorable for the tissue cells. Since this will increase the bactericidal action of the dye there can be a corresponding reduction in the strength of the latter. The value of alkalinization will depend to some extent upon its effect on the toxicity of the dyes for tissues.

Recent articles indicate that excessive alkalinization of the body is, under certain conditions, attendant with danger to the patient. This does not apply to local application. The excessive use of alkali may lead to nausea, damage to the kidneys, with associated toxemia, depletion of body salts, and other pathological conditions.²⁶ However, it appears that the administration of sufficient alkali to keep the urine decidedly alkaline over a comparatively short period of time is unlikely to produce disturbances in the average patient.

Conclusions and Summary. 1. The bacteriostatic and bactericidal action of many of the dyes varies with the hydrogen-ion concentration of the medium surrounding the organisms. With an increase in alkalinity there is, with but few exceptions, an increase in the action of the dyes for Gram-positive and Gram-negative bacteria.

2. The fluids of the body may vary in their hydrogen-ion concentration from pH 4.7 to pH 8.7 or more. The bactericidal action of the dye varies greatly within this range. The body fluids should be made alkaline by the administration of sodium bicarbonate or the application of an alkaline wash before the dye is applied.

3. Lactic acid, which is usually present in pus, reduces the action of the dyes.

4. The bacteriotropic action of the following dyes can be increased by the use of alkali: Crystal-violet, methyl-violet, gentian-violet, brilliant green, basic fuchsin, the flavins, malachite green. The action of many other dyes of less importance is affected in the same way.

5. The use of alkali will in certain types of infection prove beneficial in addition to the effect on the antiseptic power of the dyes. Controlling the hydrogen-ion concentration of the body fluids may be utilized to check the growth of certain bacteria. Many of the factors in resistance and repair, such as the leukocytes, certain enzymes, fibroblast formation, etc., are more active in an alkaline medium.

6. The action of dyes as disinfectants, methods of controlling the hydrogen-ion concentration and the dangers attendant upon alkalinization and dye therapy are discussed.

BIBLIOGRAPHY.

1. Report of Committee on Standard Methods of Examining Disinfectants, Jour. Pub. Health, 1918, 8, 506.
2. Churchman, J. W.: The Effect of Slight Increase of Temperature on the Bacteriostatic Power of Gentian Violet, Johns Hopkins Hosp. Bull., 1922, 33, 227.
3. Davis, Edwin, G.: Urinary Antisepsis, Jour. Urol., 1921, 5, 215.
4. Graham-Smith, G. S.: Some Factors Influencing the Actions of Dyes and Allied Compounds on Bacteria, Jour. Hyg., 1919, 18, 1.
5. Davis, E. G., and White, E. C.: Urinary Antisepsis: The Secretion of Antiseptic Urine following the Intravenous Administration of Acriflavin and Proflavin; a Preliminary Report, Jour. Urol., 1918, 2, 229.
6. Davis, E. G.: Urinary Antisepsis: A Study of the Antiseptic Properties and Renal Excretion of 204 Anilin Dyes, AM. JOUR. MED. SCI., 1921, 161, 251; Urinary Antisepsis: The Secretion of Antiseptic Urine by Man following the Oral Administration of Proflavin and Acriflavin; a Preliminary Report, Jour. Urol., 1921, 5, 215.
7. Browning, C. H., Gulbransen, R., and Kennaway, E. L.: Hydrogen-ion Concentration and Antiseptic Potency, with Special Reference to the Action of Acridin Compounds, Jour. Path. and Bacteriol., 1919, 23, 106.
8. Beckwith, T. D.: Studies on the Chemotherapy of the Experimental Typhoid Carrier Condition, Jour. Infect. Dis., 1921, 29, 425.
9. Kligler, I. J.: A Study of the Antiseptic Properties of Certain Organic Compounds, Jour. Exper. Med., 1918, 27, 463.
10. Burke, V.: The Gram Stain in the Diagnosis of Chronic Gonorrhea, Jour. Am. Med. Assn., 1921, 77, 1020; Notes on the Gram Stain with Description of a New Method, Jour. Bacteriol., 1922, 7, 159.

11. Kligler, I. J.: A Study of the Antiseptic Properties of Certain Organic Compounds, *Abstr. Bacteriol.*, 1918, 2, 19; *Jour. Exper. Med.*, 1918, 27, 462
- Norton, J. F., and Davis, G. E.: Bacteriostatic Action of Dyes on *Streptococcus Viridans* and *Pneumococci*, *Jour. Infect. Dis.*, 1923, 32, 220. Uhlenhuth, P., and Messerschmidt, T.: Zur Experimentellen Chemotherapie der Typhusbazillenträger und der Gallenblaseninfektionen, *Deutsch. med. Wchnschr.*, 1920, 46, 1293. Fairbrother, T. H., and Renshaw, A.: A Study of the Relation Between Antiseptic Action and Chemical Constitution in the Synthetic Aniline Dyestuffs, *Jour. Path. and Bacteriol.*, 1922, 25, 145.
12. Langer, H.: Zur Theorie der Chemotherapeutischen Leistung, *Deutsch. med. Wchnschr.*, 1920, 46, 1015.
13. Cohn, B.: Disinfection Studies: The Effect of Temperature and Hydrogen-ion Concentration upon the Viability of *Bacterium coli* and *Bacterium typhosus* in Water, *Jour. Bacteriol.*, 1922, 7, 183.
14. Cohn, B., and Clark, W. M.: The Growth of Certain Bacteria in Media of Different Hydrogen-ion Concentration, *Jour. Bacteriol.*, 1919, 4, 409.
15. Henderson, L. J., and Palmer, W. W.: On the Extremes of Variation of the Ionized Hydrogen in the Human Urine, *Jour. Biol. Chem.*, 1913, 14, 81.
16. West, R., and Stevens, F. A.: The Peptolytic Enzymes of Hemolytic *Streptococci*, *Proc. Soc. Exper. Biol. and Med.*, 1920-1921, 18, 234.
17. Cushny: *Pharmacology and Therapeutics*, Philadelphia and New York, Lea & Febiger, 1918, p. 543.
18. Nichols, H. J.: Alkaline Treatment of Early Gall-bladder Carriers, *Jour. Am. Med. Assn.*, 1917, 68, 958. Neilson, N. M., and Myer, K. F.: Bacteriostatic and Germicidal Properties of Bile, *Jour. Infect. Dis.*, 1921, 28, 542.
19. Beckwith, T. D.: The Viability and Growth of *B. Typhosus* in Bile, *Jour. Infect. Dis.*, 1921, 28, 62; The Viability of *B. Typhosus* in Alkaline Bile *in Vivo*, *Proc. Soc. Exper. Biol. and Med.*, 1920-1921, 28, 36.
20. Felton, L. D., and Daugherty, K. M.: The Organotropic, Bacteriotropic and Leukocytotropic Actions of Certain Organic Chemicals, *Jour. Exper. Med.*, 1922, 36, 163.
21. Henderson, L. J., and Palmer, W. W.: On the Extremes of Variation of the Concentration of Ionized Hydrogen in the Human Urine, *Jour. Biol. Chem.*, 1913, 14, 81.
22. *Abstr. Bacteriol.*, 5, 284.
23. Neufeld, Schiemann and Baumgarten: The Chemotherapeutic Effect of Certain Dyes in Animal Experiments with Bacterial Infections, *Abstr. Bacteriol.*, 5, 72.
24. Mueller, J. H.: Comparative Toxicity of Triphenylmethane and Flavin Dyes for Tissue and Bacteria, *Jour. Path. and Bacteriol.*, 1919, 22, 308.
25. Russel, D. G.: The Effect of Gentian Violet on Protozoa and on Tissues Growing *in Vitro*, with Special Reference to the Nucleus, *Jour. Exp. Med.*, 1914, 20, 545.
26. Editorial, *Jour. Am. Med. Assn.*, 1923, 80, 774.

THE HEMATOLOGICAL RESPONSES TO INJECTIONS OF STREPTOCOCCI.

BY LOUIS A. JULIANELLE, M.S., PH.D.,
PHILADELPHIA.

(From the Bacteriological Laboratory of the Philadelphia General Hospital.)

THE primary object of this investigation was to study the changes produced in the blood stream and hemolytopoietic organs by hemolytic streptococci; but the changes manifested were of such a nature

that a subsequent study of the changes produced by the viridans and non-hemolytic types also became necessary.

It has been observed that in streptococcus infections there is frequently a decrease in the number of erythrocytes and amount of hemoglobin, and that at autopsy the blood often seems to have undergone lytic changes. The first mentioned effect has not had sufficient study. Whether the lytic is terminal or, possibly even postmortem, has never been established; yet it has been used as evidence for hemolysis *in vivo* by streptococci.^{1 2}

We have attempted to control the experiments by obtaining definite data before the infection, and by following the progress of the infection by observations at specified intervals. In this way the results obtained offer tangible evidence regarding the presence or absence of blood destruction and bone-marrow irritation *in vivo*.

Experimental. Rabbits were used exclusively for the injections. The animals were selected on the basis of good physical condition in order to exclude as far as possible extraneous factors. Injections were made intravenously with different strains of streptococci which had been grown for fifteen to sixteen hours in meat infusion broth, the initial reaction of which was pH 7.8. The work was so arranged that one ear was used to receive the injections and the other for bleeding purposes. As a rule animals were injected several times so that the bone-marrow would produce indication of irritation or stimulation. The blood of the animals was examined several times before inoculation. This examination consisted of an enumeration of the erythrocytes and leukocytes (Levey Hemocytometer), a differential count, and an estimation of hemoglobin (Sahli). In making a differential examination of the leukocytes, smears were made in the usual manner, stained by any one of the various methods (Wright, Giemsa, Leishman), and 250 leukocytes counted. After injection, identical blood examinations were made at four, eight, and twelve hours; but later the twelve-hour examination was omitted since it did not materially add to the data. In case of *Streptococcus viridans* experiments, the serum was tested for the presence of methemoglobin by means of a microrefractometer so that the amount of serum required would be small and would not affect the red blood count. The examinations were then continued, usually every twenty-four hours after the injection.

The experiments sought to determine the effect of an infection due to: (1) A virulent and strongly hemolytic strain; (2) a highly virulent strain with hemolysis as a secondary consideration; (3) a hemolytic laboratory stock strain to produce, if possible, a subacute or chronic condition; (4) a viridans strain; (5) a non-hemolytic strain.

EXPERIMENT I. *Infection induced by a virulent and hemolytic strain; its hemolytic character being the primary consideration.*

This rabbit was inoculated with 2.5 cc of a sixteen-hour culture of a strain isolated from the blood culture of a fatal case of puerperal sepsis. Several injections were made.

TABLE I.—SHOWING THE EFFECTS OF A VIRULENT AND STRONGLY HEMOLYTIC STRAIN.

Time of examination.	Hemoglobin, per cent.	Total erythrocytes.	Total leukocytes.	Differential percentage.						Weight, gm.
				Amphophiles.	Lymphocytes.	Mononuclears.	Basophiles.	Eosinophiles.	Transitionals.	
Before injection	63	4,390,000	5,300	37.5	54.0	4	2.5	1.0	1.0	1290
4 hours after injection	50	3,860,000	6,400	70.0	25.0	3	1.0	1.0	0.0	1294
8 hours after injection	45	2,770,000	10,000	77.5	17.5	1	0.0	3.0	0.0	1290
24 hours after injection	50	4,400,000	7,800	37.5	59.5	2	0.0	0.0	1.0	1284
Before injection	48	3,900,000	8,280	43.5	41.0	3	12.0	0.0	0.0	1284
4 hours after injection	46	3,500,000	3,600	69.0	21.0	1	8.0	0.5	1.0	1274
8 hours after injection	42	2,900,000	6,400	73.0	10.0	0	5.0	0.0	12.0	1274
12 hours after injection	42	3,140,000	4,000	51.0	36.0	6	1.0	0.0	6.0	1291
24 hours after injection	42	3,410,000	5,200	38.0	41.0	0	9.0	0.0	12.0	1252
48 hours after injection	48	3,400,000	12,400	40.0	50.0	2	3.0	0.0	5.0	1200
Before injection	46	3,700,000	18,500	39.0	43.0	5	5.5	0.0	7.5	1176
4 hours after injection	46	3,760,000	12,200	43.0	45.0	1	9.0	0.0	2.0	1156
8 hours after injection	40	3,800,000	7,500	76.0	20.0	1	1.0	0.0	2.0	1156
24 hours after injection	33	3,200,000	20,600	41.0	48.0	1	6.0	0.0	4.0	1114

This animal died on the second day after the last examination (that is, lived six days). Hemolytic streptococci were recovered from the heart blood, peritoneum, spleen, and bone-marrow. Marrow from the femur was reserved for study.

This experiment was repeated with two other strains, one isolated at necropsy in a case of myocarditis; the other from a pleural fluid following pneumonia. The results were of the same nature with the exception that the leucopenia following each injection was more severe.

EXPERIMENT II. *Infection induced by a highly virulent strain; hemolysis being a secondary consideration.*

This rabbit received 2 cc of a fifteen-hour culture of a hemolytic streptococcus isolated from the gastric contents of a case of carcinoma of the stomach. The results are given in Table II.

The rabbit died between the forty-eighth and seventy-second hour. Hemolytic streptococci were recovered from cultures of the heart, peritoneum, spleen, and bone-marrow. This experiment was reproduced by the injection of a streptococcus isolated after death from endocarditis.

TABLE II.—SHOWING THE EFFECTS OF A STRONGLY VIRULENT AND HEMOLYTIC STRAIN.

Time of examination.	Hemoglobin, per cent.	Total erythrocytes.	Total leukocytes.	Differential percentage.						Weight, gm.
				Amphophiles.	Lymphocytes.	Mononuclears.	Basophiles.	Eosinophiles.	Transitionals.	
Before injection . . .	55	4,180,000	10,000	50	45	2	1	0	2	1440
4 hours after injection	48	3,910,000	7,900	80	19	1	0	0	0	1447
8 hours after injection	45	3,450,000	6,040	69	27	1	3	0	0	1443
12 hours after injection	45	3,550,000	13,600	50	32	3	11	0	4	1421
24 hours after injection	45	3,800,000	21,800	79	17	1	3	0	0	1415
48 hours after injection	45	3,900,000	17,000	68	29	1	1	0	1	1365

TABLE III.—SHOWING THE EFFECTS OF A LABORATORY STRAIN (HEMOLYTIC).

Time of examination.	Hemoglobin, per cent.	Total erythrocytes.	Total leukocytes.	Differential percentage.						Weight, gm.
				Amphophiles.	Lymphocytes.	Mononuclears.	Basophiles.	Eosinophiles.	Transitionals.	
Before injection . . .	85	5,200,000	5,100	40	51	7	1	1	0	
1 day after injection . .	61	5,270,000	9,400	45	39	7	4	1	3	
2 days after injection . .	50	4,500,000	8,200	45	39	4	7	0	3	
1 day after injection . .	50	5,400,000	8,200	53	30	4	6	0	5	
2 days after injection . .	46	4,800,000	13,800	46	42	4	5	1	4	
3 days after injection . .	46	4,750,000	7,800	58	33	1	7	1	0	
Before injection . . .	52	5,400,000	8,200	58	43	4	3	0	2	
1 day after injection . .	52	4,470,000	8,200	58	38	3	6	0	0	
2 days after injection . .	52	5,200,000	7,800	38	51	4	4	0	2	
3 days after injection . .	57	5,230,000	17,500	71	21	0	4	0	4	
Before injection . . .	58	5,450,000	7,400	45	49	2	1	0	3	
1 day after injection . .	56	5,280,000	4,600	45	49	2	1	0	3	
2 days after injection . .	56	5,760,000	8,400	54	42	2	1	0	1	
Before injection . . .	60	5,700,000	9,200	45	51	2	0	0	2	
1 day after injection . .	64	5,660,000	5,600	37	60	0	1	0	2	
4 days after injection . .	70	7,000,000	12,000	40	53	2	3	1	1	

EXPERIMENT III. *Infection induced by a laboratory strain to approximate a subacute or chronic condition in man.*

This strain was isolated more than a year ago from pus. It has a high hemolytic titer, and we assumed its virulence to be of a

low grade. Broth cultures (incubated fifteen to sixteen hours) were injected intravenously in 1 cc amounts, and the injections were continued regularly twice a week for about three weeks.

The animal died one day after the final blood examination (that is, lived twenty-eight days). Hemolytic streptococci were recovered from the peritoneum, heart blood, spleen and bone-marrow.

Analysis of the Effects of Hemolytic Streptococcus Injections. A study of the tables shows several facts. In the first place there is a loss of erythrocytes accompanied by a concomitant decrease in hemoglobin. This loss is rapid and extensive, usually taking place within eight hours, and in some cases constituting 50 per cent of the original number of red cells. But this reaction is transient and within twenty-four hours the number of erythrocytes is approximately normal. The hemoglobin, although tending to return toward normal, never reaches the normal. This is particularly true after the first injection, but as the injections are continued the loss of blood cells becomes progressively less, so that the level remains relatively constant. At the termination of the experiment the number of red cells is appreciably less than at the beginning. In Experiment I, these results are clearly demonstrated; but if the strain happens to be too virulent, the hemolytic effect is either masked or is of less degree because death occurs too soon for any great changes. On the other hand, a non-virulent strain produces only a slight decrease in erythrocytes.

Just as significant are the leukocyte reactions. The general rule is, first a decided leukopenia, in some instances to 70 per cent of the normal. The period of leukopenia varies but usually reaches its lowest in eight hours. This is followed by a sharp leukocytosis; the leukocytes manifest this reaction with each succeeding injection of the streptococci, and if anything the leukopenia becomes more accentuated. The differential count shows a decided preponderance of amphophiles (the counterpart of polymorphonuclears of the human blood) frequently reaching 80 per cent or more. This is especially significant when one considers that normally rabbits show 40 to 50 per cent amphophiles. The sudden appearance and disappearance of basophiles is puzzling. They fluctuate within wide limits, and their fluctuations are not interpretable in terms of frequency or corelationship to any of the controllable factors.

The weights of the animals show many variations, which do not appear associated with loss or recovery of blood cells. In those animals which ultimately succumb the mean of the weight curve tends lower and lower; in cases of recovery from the infection, the weight lost is gradually regained.

When the infection extended over a prolonged period blood destruction was evident in the blood smears as in Experiments I and III. Anisocytosis and poikilocytosis generally appeared, the former preceding, and polychromatophilia also occurred. Occasionally

normoblasts were discovered, though it must be said that their number never exceeded 3 per cent and they appeared and disappeared in an unexplainable way. Leukocytes were often found that had undergone disintegration, but there was a doubt as to whether this was a result of the injections or mechanical. Myelocytes, in small numbers, were seen occasionally. In some of the four-hour smears, streptococci were often present, both unattached and within white cells. When death occurred shortly after the injection (Experiment II), the smears were normal except for the differential percentage.

The marrow reactions were by far the most important produced and were distinctive of the type of infection.

In Experiment I the marrow suggested a hypoplastic condition. There was apparently an extensive destruction of both red and white cells. The cells that were present stained poorly and were undergoing swelling and karyorrhexis. Some leukoblasts and primordial red cells were distinguished, but no eosinophiles nor basophiles were discoverable. The general appearance suggested that there had been a powerful irritation followed by an exhaustion of the erythropoietic organs.

The changes of the second type of infection were distinctive of an extremely toxic condition. Eosinophiles predominated and most of them were undergoing degeneration. A fair number of normal erythrocytes were present, so that it would seem that the toxic rather than the hemolytic character of the streptococci injected was the most important factor. Karyokinesis was observed in occasional cells.

The third type showed an actively progressing regeneration. There were nucleated erythrocytes in all stages, and karyokinetic cells were frequent. There were no changes in the leukocytic cells and the eosinophiles were not abnormally numerous. In short the picture was one of active hemopoiesis.

It is evident that hemolytic streptococci exert a destructive influence on erythrocytes and leukocytes. In order to show that this action is specific and not perhaps due to a foreign body, or a redistribution of the blood away from the peripheral circulation, and so on, rabbits were injected with cultures of *Streptococcus viridans* in one case, and non-hemolytic streptococcus in the other.

EXPERIMENT IV. *Infection induced with Streptococcus viridans.*

This strain was isolated from a pneumonic sputum and 3 cc of a sixteen-hour culture was injected. The results are presented in Table IV.

EXPERIMENT V. *Infection induced with a non-hemolytic strain* (Table V).

This strain was isolated from a human blood culture, a few days preceding death. Three cubic centimeters of a sixteen-hour culture were injected.

TABLE IV.—SHOWING THE EFFECTS OF VIRIDANS STRAIN.

Time of examination.	Hemoglobin, per cent.	Total erythrocytes.	Total leukocytes.	Differential percentage.						Weight, gm.
				Amphophiles.	Lymphocytes.	Mononuclears.	Basophiles.	Eosinophiles.	Transitionals.	
Before injection . . .	80	5,400,000	7,400	32	60	3	5	0	0	1872
4 hours after injection	77	5,420,000	5,000	74	19	0	5	0	0	1872
8 hours after injection	65	4,890,000	4,500	76	16	0	7	0	0	2020
24 hours after injection	75	5,350,000	7,300	46	48	1	5	0	1	1875
Before injection . . .	75	6,360,000	15,400	35	57	2	4	0	0	1880
4 hours after injection	75	6,480,000	4,640	30	59	1	7	0	4	1896
8 hours after injection	70	5,650,000	20,200	53	39	0	7	1	2	1896
12 hours after injection	75	5,470,000	6,900	45	49	1	3	2	3	1898
24 hours after injection	78	5,800,000	8,600	35	49	3	8	0	1	1908
Before injection . . .	75	5,400,000	9,200	41	48	4	5	0	2	1910
4 hours after injection	75	5,290,000	6,800	78	14	1	4	0	1	1910
8 hours after injection	70	4,750,000	5,000	75	18	1	4	3	0	1916
24 hours after injection	75	5,380,000	14,800	51	27	4	16	2	0	1880

(This rabbit did not die.)

TABLE V.—SHOWING EFFECTS OF NON-HEMOLYTIC STRAIN.

Time of examination.	Hemoglobin, per cent.	Total erythrocytes.	Total leukocytes.	Differential percentage.						Weight, gm.
				Amphophiles.	Lymphocytes.	Mononuclears.	Basophiles.	Eosinophiles.	Transitionals.	
Before injection . . .	65	4,280,000	8,600	48	51	1	0	0	0	2060
4 hours after injection	63	4,400,000	4,400	60	37	2	1	0	0	2052
8 hours after injection	63	4,010,000	7,500	70	24	2	3	0	1	2030
24 hours after injection	65	5,130,000	9,500	62	25	1	7	0	0	1980
48 hours after injection	65	4,340,000	9,300	66	26	1	3	1	3	2050
96 hours after injection	X	4,960,000	11,600	45	45	1	5	1	2	1900
Before injection . . .	68	4,720,000	8,000	40	46	5	4	0	2	1955
4 hours after injection	68	5,100,000	4,000	76	18	1	4	1	0	1916
24 hours after injection	68	5,030,000	6,400	36	46	6	12	0	0	1957
48 hours after injection	65	5,100,000	10,500	24	63	3	3	0	7	2079
5 days after injection .	65	4,870,000	8,200	33	60	2	2	0	3	2160
7 days after injection .	65	4,280,000	6,000	33	60	1	4	0	2	2185
Before injection . . .	68	5,430,000	7,100	35	60	0	5	0	0	2100
6 hours after injection	60	4,910,000	2,300	76	17	0	7	0	0	2185
24 hours after injection	60	4,750,000	6,000	26	68	1	5	0	0	1933
96 hours after injection	60	4,510,000	10,600	27	70	1	2	0	0	2005

(This rabbit did not die.)

The experiment with *Streptococcus viridans* was repeated with a strain from pus, and showed more or less the same tendency; with the repetition of the non-hemolytic experiment queer results were obtained. In one case, the rabbit responded as shown in Table V; but in the other instance, an anemic condition was produced, a decided destruction of red cells, a decrease in hemoglobin, anisocytosis, poikilocytosis, polychromatophilia, a discharge into the circulation of nucleated reds, and what appeared to be basophilic megablasts. These results were so different from those obtained in the other two similar experiments and so unexplainable that it was felt that they were probably referable to some preëxisting condition in this animal.

To summarize Experiment IV, it can be stated that the destruction of red cells and the decrease in hemoglobin are slight. There seems to be a slight loss in erythrocytes within eight hours, but it is not large enough to be definite. The leukocytes show the same picture as in the case of hemolytic streptococcus injections. Methemoglobin was not demonstrated in the serum.

In Experiment V the red blood cells and hemoglobin do not appear to have been affected by the organisms injected. The slight changes were within the normal variations. The leukocytes show a leukopenia, followed by a leukocytosis with a preponderance of amphophiles. The basophiles in Experiments IV and V show a similar inexplainable appearance and disappearance as in the case of hemolytic streptococcus injections.

Discussion. In this discussion, two points must be borne in mind: first, that as injections of organisms are repeated, the animal is becoming more and more immune; and second, that an originally virulent strain loses its virulence as it is kept on laboratory media. The result is that the first injection may show enormous changes in the blood picture, while subsequent injections may show progressively less changes until perhaps there are no longer apparent effects. In attempting to produce a chronic condition (as in Experiment III), this difficulty was particularly encountered. The animal no longer showed response to the injections and as a matter of fact eventually compensated for the original loss of erythrocytes; then as the injections were continued, no further changes were obtainable.

It is patent that blood destruction may accompany injections of hemolytic streptococci. It cannot be considered as due to a redistribution of the blood away from the peripheral circulation, nor to a foreign body reaction. The fifth experiment with non-hemolytic streptococci shows clearly that the reaction is peculiar to those cocci which possess the ability to destroy blood. This blood destruction we regard as referable to the soluble hemolysin contained in the cultures. First the cultures used were young, and as De Kruif and Ireland³ have shown, it is from such cultures that the greatest yield

of hemolysin is obtained. Secondly, the destruction was rapid and was succeeded by a compensatory reaction which might indicate that the hemolysin contained in the broth culture was eliminated from the circulation, bringing the lytic action to an end. It is quite true that Hopkins and Parker⁴ demonstrated that streptococci injected into the blood stream are no longer recoverable after a few hours, but their reappearance is equally positive. After the first destruction of red cells, there is an overproduction tending to bring the count toward the normal, despite the fact that streptococci are still in the circulation. The increase in number of erythrocytes before death (as in Experiment III) is possibly explained by dehydration due to fever, combined with lack of food and water intake, concentrating the blood constituents.

The hemoglobin decreased, though not proportionately with the red cells. But after the initial destruction of cells, an increase in their number was never accompanied by a corresponding increase in hemoglobin. This is explainable on the grounds that in cases of rapid destruction of red cells, there is regeneration of an abnormally large number of cells, which do not contain normal amounts of hemoglobin.

The leukopenia reported here had already been observed by Hopkins and Parker⁴ and Tongs.⁵ This leukopenia is accounted for, we think, partly by the presence of a leukocidin in the cultures used for the injections. It has been clearly shown by Nakayama⁶ that ten- to twenty-four-hour cultures contain a leukocidin, although the presence of such a substance had long been suggested by Ruediger,⁷ Hektoen,⁸ McLeod⁹ and others. Tongs, also, suspecting a leukocidin responsible for this leukopenia demonstrated micro- and macroscopically that his cultures (twenty-four hours old) contained this toxic material. There is another possibility which may contribute to the leukopenia. The injection of a foreign body may draw the leukocytes from the peripheral circulation within a few hours and then produce a discharge of the leukocytes plus newly generated ones, thereby producing the leukocytosis. Such an assumption better explains such a case as Experiment V, where no action on the blood (except for this one of leukopenia) can be demonstrated either *in vitro* or *in vivo*.

The types of red and white cells observed by smear are of interest. The red cells show in some cases extreme variations in shape, size and ability to take the basic stains, thereby suggesting anemic changes. We should hesitate to state, however, that these changes are anemic. Fishel and Adler¹⁰ reported that they were able to produce pernicious anemia with a hemolytic streptococcus isolated from a human case with this diagnosis. Normal rabbits frequently show these atypical red cells, so that their appearance is not necessarily significant. The fact that the number of red cells decreases so much and no more, that nucleated reds in the circulation are

few, that the more embryonic reds are very rarely seen, and that an immunity is developed, leads us to surmise that a chronic clinical anemia produced by streptococci would be a very unusual thing.

The basophiles in the smears examined were beyond explanation by us. We could not coördinate either their sudden increase or their sudden decrease and disappearance. Basophiles normally are present in rabbit's blood averaging about 6 per cent, but increases to 12 to 15 per cent and a decrease to 0 were common.

The bone-marrow offered the best field for study. It acted in a sensitive way to the injections and perhaps explained the reactions taking place most clearly. It would appear that hemolytic streptococci will produce blood destruction *in vivo* provided the strain used is virulent or the dosage of an avirulent strain is extremely large. If the strain is excessively virulent, the destruction is not marked (due to rapid death). When death occurs it is probably caused by a toxemia plus blood destruction, rather than blood destruction alone.

Summary. Rabbits were injected with different strains of streptococci to determine their effect on the blood. Three types of infections were attempted with hemolytic streptococci and these were controlled by injections of the viridans and non-hemolytic types.

Hemolysis occurred *in vivo* by injection of young cultures of *Streptococcus hemolyticus*. Virulent hemolytic strains produced the best examples; strongly virulent strain produced death rapidly and the blood changes were less extensive; with a laboratory strain, the changes produced were the best of the three types.

Viridans strains produced slight hemolysis.

Non-hemolytic strains did not produce blood destruction.

All three types of streptococci produced first a leukopenia which was followed by a leukocytosis. The leukopenia was due either to the presence of leukocidin, or to a foreign body reaction, or perhaps to a combination of both. The leukocytosis showed a preponderance of amphophiles.

Basophiles appeared and disappeared in an unexplainable way in the blood smears.

The marrow offered the clearest picture regarding blood destruction, blood regeneration and toxic effect of the streptococci injected.

Since going to press, we have determined more definitely the nature of the blood destruction and leukopenia. Sterile filtered cultures of hemolytic streptococcus in two out of five instances produced a decrease in red cells and hemoglobin. This reaction was not so extensive nor of so long duration as when whole cultures were injected.

Rabbits injected with foreign protein, such as horse serum, typhoid vaccine, Coley's fluid and casein showed the same type of leukocyte changes as did the cultures of streptococci. We believe, therefore, that the leukopenia and leukocytosis are foreign protein reactions rather than specific of streptococci.

REFERENCES.

1. Bordet: Ann. de l'Inst. Pasteur, 1897, 11, 178.
2. Besredka: Ann. de l'Inst. Pasteur, 1901, 15, 880.
3. De Kruif and Ireland: Jour. Infect. Dis., 1920, 26, 285.
4. Hopkins and Parker: Jour. Exper. Med., 1918, 27, 1.
5. Tongs: Jour. Infect. Dis., 1921, 29, 141.
6. Nakayama: Jour. Infect. Dis., 1920, 27, 86.
7. Ruediger: Jour. Am. Med. Assn., 1905, 44, 198.
8. Hektoen: Jour. Am. Med. Assn., 1906, 46, 1407.
9. McLeod: Jour. Path. and Bacteriol., 1915, 19, 392.
10. Fishel and Adler: Centralbl. f. Bacteriol., 1894, 15, 24.

REVIEWS.

A MANUAL OF CHEMISTRY. By W. SIMON, PH.D., M.D., late Professor of Chemistry, College of Physicians and Surgeons of Baltimore; and DANIEL BASE, PH.D., formerly Professor of Chemistry, Maryland College of Pharmacy. Twelfth edition. Pp. 667; 55 engravings and 7 colored plates. Philadelphia: Lea & Febiger, 1923.

IN the words of the preface, "The object of this manual is to furnish to the student in concise form a clear presentation of the science, an intelligent discussion of those substances which are of interest to him, and a trustworthy guide to his work in the laboratory." After a short section on the fundamental properties of physics and on heat (under the head of Chemical Physics) the book is divided into sections of General Chemistry (303 pages), Analytical Chemistry (70 pages) and Organic Chemistry (209 pages). It should be a valuable help to students of medicine, pharmacy and dentistry, for whom it has been especially adapted. K.

GREEN'S MANUAL OF PATHOLOGY AND MORBID ANATOMY. Revised and enlarged by W. CECIL BOSANQUET, M.D., F.R.C.P., Physician to Charing Cross Hospital; and G. B. WILSON, M.D., M.R.C.P., Demonstrator in Bacteriology, Charing Cross Hospital Medical School. Thirteenth edition. Pp. 624; 244 illustrations. Philadelphia: Lea & Febiger, 1923.

ANY medical book that has reached its thirteenth edition must *ipso facto* possess marked intrinsic value. In the present case we suspect that this value must be largely in the excellent reputation of the early editions and in the attractive form in which this edition is presented. The illustrations are examples of the latter virtue, especially those from the C. C. H. museum; but, on the other hand, too many are from the Ziegler-Rindfleisch era. Unless the difference in teaching pathology in Great Britain and in this country is greater than commonly thought, the book should seem old-fashioned and not sufficiently up to date to readers of both

countries. For instance, the only mention of the glands of internal secretion is found under the head of "auto-intoxications," where the pituitary is dismissed in 14 lines, the ovaries in 13, the testicles in 6—exactly the same number as is devoted to "sapremia," though it is admitted on page 292 that "pure sapremia . . . rarely, if ever, occurs, and the term has little real significance." More than 100 pages are devoted to bacteriology and immunity, which causes all of special pathology to be condensed into 206 pages. Diseases of the spleen are thus dismissed in less than a page, functional disorders of the heart in a half-page (of which the arrhythmias get 9 lines) and so on. Although such criticisms lose force when applied to a manual, we feel that they correctly emphasize its value relative to more complete books. For those who desire the smaller kind, this book is not without merit.

K.

PRURITUS OF THE PERINEUM. By JOSEPH FRANKLIN MONTAGUE, M.D., of the Rectal Clinic, University and Bellevue Hospital Medical College; Fellow American Proctologic Society and New York Pathological Society. Foreword by DR. GEORGE DAVID STEWART, President of the New York Academy of Medicine. Pp. 181; 37 illustrations. New York: Paul B. Hoeber, 1923.

ANYONE who has struggled with the treatment of pruritus of the anus and vulva will welcome a small monograph devoted to the condition. There is a wealth of information on the history, pathology, etiology, clinical characteristics and treatment. The author defines two groups; namely, indirect pruritus and direct pruritus. The book is devoted largely to elucidating his concept of indirect pruritus which is his contribution to the etiology. This form of itching is due, according to his ideas, "to the perception of the pruritic sensation which in consciousness is referred to the pruritic zone, an area which is at the inception of the pruritus devoid of any pathology at all. This phenomenon is due to the transference of an irritable stimulus from the visceral afferent nerves to a normal somatic afferent nerve channel or pathway and the consequent misreference or error in localization." This concept is, naturally, impossible of definite proof or disproof but is supported by analogy and clinical instances of cure by removal of visceral disease. It has the merit of demanding thorough general examination and treatment. Direct pruritus is dependent upon local disease and may follow indirect pruritus as a result of trauma from scratching or irritating applications. Treatment is fully considered and a complete bibliography is appended.

P.

HIGH BLOOD-PRESSURE: ITS VARIATIONS AND CONTROL. By J. F. HALLS DALLY, M.A., M.D., B.C. (CANTAB.), M.R.C.P. (LOND.), Physician to the Mount Vernon Hospital for Tuberculosis and Diseases of the Heart. Pp. 155; 23 illustrations. New York: William Wood & Co., 1924.

THIS work deals with the clinical estimation of the arterial pressure, and the etiology, pathology and treatment of hypertension. The importance of the diastolic pressure is emphasized throughout, and the evidence is reviewed upon which the end of the third phase is taken as the true index of the diastolic pressures. A bibliography of 193 references concludes the book. Even though one may question the need for another book upon hypertension at this time when so little is known regarding its cause or cure, nevertheless the practitioner or student will find in these pages a brief and satisfactory review of our present knowledge of the subject. A.

A CLINICAL GUIDE TO BEDSIDE EXAMINATION. By H. ELIAS, M.D., Dozent and Assistant at the First Medical Clinic of the University of Vienna, Austria; N. Jagic, M.D., Extraordinary Professor and Chief Physician to the Sofienspital, Vienna, Austria; and A. Luger, M.D., Dozent and Assistant at the Second Medical Clinic of the University of Vienna, Austria. Arranged and translated by WILLIAM A. BRAMS, M.D., Chicago, Ill., Adjunct in Medicine, Michael Reese Hospital. Pp. 135. New York City: Rebman Company, 1923.

THIS little book takes up physical examination of the patient systematically. It would be of value to hospital residents and medical students, during the last two years of their course, in teaching them how to make a thorough and complete physical examination. M.

HANDBOOK FOR MENTAL NURSES. Published under the authority of the Medico-Psychological Association. Seventh edition. Pp. 615; illustrated. Chicago: Chicago Medical Book Company, 1923.

THIS text-book, primarily for attendants in mental institutions, has much information for all nurses. While the major portion is devoted to the nervous system, its anatomy, physiology and nervous and mental disorders, the forepart of the book deals with nursing knowledge necessary for somatic disorders. The volume serves well its purpose. B.

THE OPHTHALMIC YEAR BOOK, 1923. Vol. XIX. Edited by EDWARD JACKSON and WILLIAM H. CRISP. Pp. 367. Chicago: The Ophthalmic Publishing Company, 1923.

THIS collaborated volume brings up the references to the current literature of ophthalmology through December, 1922. The chapter on Comparative Ophthalmology covers the period since 1916. Material is grouped under major headings with appropriate subdivisions, each chapter prefaced by a bibliography, following which the publications of individual workers are abstracted and summarized. The volume has been carefully edited and is an invaluable reference work for all students of ophthalmology.

I.

PRACTICAL MEDICINE SERIES. Vol. I. General Medicine. Series, 1923. Under the general editorial charge of CHARLES L. MIX, A.M., M.D. Pp. 678. Chicago: The Year Book Publishers, 1923.

THE volume on General Medicine of Practical Medicine Series for 1923 continues to follow the high standards set by the previous editions. One could hardly expect other than this when the list of editors is made up of such distinguished clinicians as Weaver, Lawrason Brown, Preble and Sippy and Ralph Brown. M.

METHODS IN MEDICINE: MEDICAL SERVICE OF GEORGE DOCK. By GEORGE R. HERRMANN, M.D., PH.D., Instructor in Medicine, University of Michigan; formerly House Officer, Peter Bent Brigham Hospital, Boston. Pp. 521; illustrated. St. Louis: C. V. Mosby Company, 1924.

THIS manual outlines in detail the various methods that are applied to the proper running of a medical service. The first section includes notes on the duties of a resident physician, assistant resident physician, the interns, record-room rules, roentgen-ray department rules, superintendent's rules and so on. The author then takes up the question of history-taking and physical examination and follows that with a long section on laboratory tests. Following this are sections on diets, succeeding which there is a portion of the book devoted to therapeutic methods and lastly apparently the whole series of charts that are used in the Barnes Hospital. In analyzing a book of this type it must be borne in mind that it has as its function the purpose of teaching the younger medical

man; more particularly the senior student and the junior intern. For that reason a large portion of it is of little value to the more mature clinician. However, the part that is of value to such an individual is of special value because it outlines to him various tests and laboratory procedures that might be difficult to find in the ordinary literature and difficult to remember from student days. To the reviewer there are two criticisms that seem pertinent. In the first place he believes that the section on history taking and physical examination is entirely too short and that the author could very easily incorporate a goodly portion of the "outlines of case-taking" by Doctor Dock in his Chapter VIII to the betterment of the work and he could do so by limiting the space devoted to the laboratory and chemical methods. Lastly, the reviewer hardly sees the necessity of placing on permanent record a large number of hospital charts, blanks and forms which occupy nearly a hundred pages of the book. With the exception of the above criticisms the book is first-class. It is a book teeming with practical points in the management of a hospital medical service and could be very well kept for reference in every hospital that does not have a technic book of its own.

M.

GERIATRICS. By MALFORD W. THEWLIS, M.D., Editor, *Medical Review of Reviews*; Associate Editor, *The Therapeutic and Dietetic Age*. Second edition. Pp. 401; 24 illustrations. St. Louis: C. V. Mosby Company, 1924.

THE second edition of this book has been considerably revised and several new chapters added. The book is interesting, but one cannot help but feeling that it is rather hastily written in spite of the revisions, and that it does not go sufficiently deep or critically into the subject. For example, we doubt very much indeed if hepatic extract is of value in the treatment of liver disease and prostatic extract is of value in prostatic disease.

M.

GESCHICHTE DER MEDIZIN. By PROF. DR. PAUL DIEPGEN, Honorary Professor of the History of Medicine in Freiburg. Second edition. Pp. 131. Berlin and Leipsic: Walter de Gruyter & Co., 1923.

IN the ten years since the appearance of the first edition of this work researches in medical history have made notable progress, especially in our knowledge of ancient medicine. These have been adequately treated in the new edition. The lives of individual preëminent physicians have been alluded to in greater detail. The book represents a brief, concise and withal illuminating presentation of the subject.

K.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI,
CINCINNATI, OHIO.

Cutaneous Hypersensitiveness in Enteric Infections with Special Reference to Enteric Carriers.—The recognition of enteric carriers frequently offers such difficulties that the suggestion given by McKENDRICK (*Jour. Path. and Bact.*, 1923, 26, 535) for testing the suspected persons for cutaneous hypersensitivity to the typhoid group deserves earnest consideration. He investigated the following series of cases, using standard suspensions of the killed organisms: 5 chronic carriers, 14 cases of enteric fever, 19 persons who had undergone prophylactic inoculation and 2 with a previous history of infection; and in addition 360 control cases in none of whom was there history of enteric fever or prophylactic inoculation. Positive reactions were uniformly obtained in patients with enteric fever (up to the beginning of convalescence) and in chronic carriers. The tests seem to be highly specific since only suspensions of the type of organisms demonstrated in the feces would give positive skin reactions. Only 2 out of 360 control cases gave positive reactions, while all patients having had previous inoculation or the infection itself reacted negatively. One patient, while apparently convalescent from typhoid, continued to react positively; it is interesting to note that this patient suffered two relapses. It is suggested that all patients convalescing from enteric fever be examined for the skin reaction in addition to stool examinations, as the latter may often fail to aid in detecting carriers.

The Prevalence and Trend of Drug Addiction in the United States and Factors Influencing it.—KOLB and DU MEZ (*Public Health Reports*, 1924, 39, 1179) have made an extensive study of the number of drug addicts that are present in the United States at the present time. From their statistics they hold that there are approximately 150,000 as a maximum

estimate, but they believe that 110,000 is a number more nearly correct. The addicts have steadily decreased since 1900 so that at the present time there has been a decrease of over 50 per cent, and this in spite of the fact that there are a large number of addicts in prison, more than there were twenty-five years ago, due to the more thorough enforcement of the laws of the country in respect to the use of opiates. The average daily addiction dose of morphin sulphate, heroin hydrochlorid and cocain hydrochlorid is not less than six grains. The use of opium and laudanum has been almost entirely abolished while cocain hydrochlorid is used only in conjunction with opiates excepting in a rare case. The actual known quantity of narcotics imported by the United States at the present time is only slightly in excess of that required to supply medicinal needs. While these figures are, of course, authentic, it does not by any means include the large quantities of these drugs which presumably are smuggled into the country. One pleasant feature of their study was the fact that doctors who had been so frequently incriminated as causing drug habit in patients, actually are responsible for only a very few cases and not all these can be substantiated. There can be no question that patients are in the habit of blaming physicians rather than their own inherent weakness when their sole purpose is to secure sympathy for their vice. The authors feel that as a result of the attention given to the problem by the medical profession and law enforcing officers that not many years distant the few remaining addicts will be persons taking opium because of an incurable disease and addicts of the psychopathic type who spend a great part of their time in prison.

The Pathogenesis of Primary Pneumococcal Peritonitis.—In a previous paper, McCARTNEY and FRASER, (*Brit. Jour. of Surg.*, 1922, 9, 479) clinical evidence was brought forth that primary pneumococcal peritonitis occurs only in females, mainly between the ages of two and eleven years. Of 56 cases of pneumococcal peritonitis studied by them, 36 were primary and 20 secondary. All of the 36 primary cases occurred in girls from two to eleven years old. Of the secondary cases, 12 were in boys and 8 in girls. The symptoms of the primary form were always first those of pelvic inflammation, and early operation disclosed only the pelvic peritoneum involved, frequently localized in the region near the opening of the Fallopian tubes. In the present paper McCARTNEY (*Jour. Path. and Bact.*, 1923, 26, 507) reports his studies on 10 primary cases (girls three and a quarter to six and a half years old). In all the cases the same type organism was cultured from the vagina as from the blood and peritoneal cavity. Only 6 of the 10 gave positive throat cultures, 1 of which was of Type IV, while Type I was found in the peritoneal cavity, blood and vagina. The vaginal flora of 150 children of the poorer class (to which class this form of peritonitis is nearly always limited) was studied over a period of one and a half years. Pneumococci could frequently be isolated, usually non-pathogenic Type IV strains, but on several occasions Type I was found. Pneumococci could not be demonstrated in the vaginal secretions of well-cared-for children. Vaginitis with an alkaline secretion, so often present among children of the poorer classes in the summer seems to favor the pneumococcal infection. Experimental production of the disease was successful only in the young female monkey. Here one of three

monkeys developed the typical pelvic peritonitis following inoculation of Type II pneumococcus broth into the vagina. The inflammation was most severe in the pelvis although the uterus and tubes presented nothing abnormal. The original culture was recovered from the peritoneal cavity and from the Fallopian tubes. The conclusion is reached that primary pneumococcal peritonitis is caused by an ascending infection coming from the vagina.

Roentgen-Ray Intoxication.—In a series of interesting papers, WARREN and WHIPPLE (*Jour. Exper. Med.*, 1924, 38, 713) set forth the effects produced in animals by roentgen-ray destruction of the intestinal epithelium. Contrary to the prevailing idea that this epithelium is the barrier excluding intestinal bacteria from entrance into the blood stream, these authors find that its complete destruction does not lead to any bacterial invasion, until just preceding death. A profuse excretion of fluid into the intestinal lumen with vomiting and diarrhea accompanies the desquamation, however, so that this out-flowing current may be one factor preventing such invasion. The conditions might possibly be quite different if active absorption could be induced along with the desquamation. The sensitivity of the intestinal epithelium to the rays should always be considered in treatment of abdominal or pelvic condition by radiation according to the authors. Intestinal lesions may be produced which may be repaired completely or may go on to form permanent ulcers. They were able to produce in animals ulcers which resisted healing as do peptic, duodenal, and other chronic intestinal ulcers. The small intestinal mucosa was found to be much more sensitive to injury than that of the stomach or colon.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND
ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES
IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SUR-
GEON TO THE PHILADELPHIA GENERAL AND
NORTHEASTERN HOSPITALS.

Chronic Vesical Distention.—SHAW and YOUNG (*Jour. Urol.*, 1924, 11, 373) say that immediate and continuous bladder drainage is followed by a more or less severe reaction in the majority of cases of chronic urinary obstructions. The reaction may be predominantly renal, circulatory or nervous, but, usually there are symptoms referable to all three systems. The reaction in the urinary tract is the most constant and is shown by bleeding from the bladder and kidneys, the appearance of albumin and casts in the urine, and frequently an abrupt fall in the renal function as shown by the phthalein test and blood

chemistry studies. All these symptoms may be present without any change in the blood-pressure. Sudden reduction of increased vesical tension, renders the kidneys more susceptible to infection. The reaction in the circulatory system occurs less frequently but may be quite severe. Complete suppression of urine occurs as a result of the lowered blood-pressure. The present study does not show that the blood-pressure is regularly increased in prostatic hypertrophy, even when accompanied by marked chronic vesical distention. Mild nervous and mental symptoms, frequently follow sudden drainage of the overdistended bladder. These symptoms may occur without any changes in the blood chemistry. By gradually reducing the bladder pressure, the reaction can be avoided in most cases.

The Causes and Changes in Loose Bodies Arising from the Articular Surface of the Joint.—PHEMISTER (*Jour. Bone and Joint Surg.*, 1924, 6, 278) says that the lesion does not seem to be a complete intra-articular fracture. Nutritional disturbance in the partially detached portion would favor the occurrence of non-union. Primary necrosis of the portion which becomes detached has been shown not to occur in at least a certain percentage of cases. After the body becomes loosened, degenerative and regenerative changes go on in it, both while it is attached by a pedicle and after it is completely liberated in the joint.

Mechanism of the Normal and of the Flat Foot.—MORTON (*Jour. Bone and Joint Surg.*, 1924, 6, 368) says that flatfoot is essentially and primarily a faulty posture of the os calcis, by which an improper distribution of body weight and muscle force is transmitted to the fore part of the foot through its two channels, the scaphoid and cuboid bones. In the fore part of the foot, functional derangement is purely secondary to the improper distribution of forces thrown upon it from the posterior half. There is a loss of the normal balance of the forces passing through the foot, so that the unbalanced structure is caused to roll inward (pronate). The plantar ligaments are the only real weight supporting soft structures of the foot. The lateral muscles and ligaments are merely controlling in their actions and incapable of sustaining any considerable amount of body weight. The early movement of the faulty posture is almost directly lateral; the resulting progressive slant, however, of the calcaneal facets causes an inward shifting of body weight and the creation of a strong lateral thrust, which together constitute an overpowering burden upon the relatively weak lateral structures. This burden is termed a "false load," because it is a new and abnormal element of strain thrown upon lateral structures and by them is merely transmitted back again upon the leg and foot. Bone changes ultimately occur, which accord with the disordered movements of force and the uneven contact of joint surfaces.

The Renal Circulation.—LEE-BROWN (*Arch. Surg.*, 1924, 8, 831) says that the coarse distribution of the renal vessels conforms to the generally accepted teaching. The atrophic or aborted glomeruli are found in close proximity to the medulla and represent glomeruli devoid of a capsule and whose specific function has ceased. The arterial rectæ originate as efferent vessels from glomeruli situated chiefly in

close relationship with the medulla. These vessels form the chief blood supply of the medulla. There are four distinct types of efferent vessels, subcapsular, cortical, cortico-medullary and medullary. All branches of the renal artery are not true end arteries, as a return flow may be obtained by way of the posterior division when the organ is irrigated with physiologic sodium chlorid solution through the anterior division of the artery. The renal circulation is irreversible. All findings have been actually observed and are individually substantiated by direct photographs.

Some Problems of Jaundice and Their Significance in Surgery.—

DE TAKATS (*Ann. Surg.*, 1924, 79, 662) says two groups of jaundice can be distinguished that are best called cholemia and bilirubinemia. The first is caused by any disturbance in the bileflow, or by the incompetency of the hepatic cell; the latter is an overproduction of bilirubin, in consequence of an increased degree of hemolysis. The intact liver function is of high importance for the surgeon. Its disturbance will produce longer bleeding and coagulation time, a greater susceptibility for narcotics and a marked acidosis after the operation. In consideration of the imminent dangers of cholemia, these patients should be submitted to operation as soon as possible. Jaundice of hemolytic origin can be cured by splenectomy, although one might not always succeed in healing the actual disease. In cases of thrombopenia, the hemorrhage ceases after splenectomy, although the increase of blood platelets is only temporary.

Duodenal Ulcer Among Medical Men: A Comparison of the Results of Surgical and Medical Treatment.—FORSYTH (*Brit. Med. Jour.*, 1924, 1, 780) says there was no mortality in non-operated cases. Two of 3 deaths in operated cases, immediately followed operation. The absence of deaths among the non-operated cases is noteworthy, seeing that hemorrhage is noted fairly often. The special value of these figures, extracted from the registers of the Medical Sickness Society, is that they represent a business, and therefore impartial record of the after histories of the cases. They show that duodenal ulceration entails long periods of sickness and though not often mortal, is very liable to recur, even after many years; but the majority of cases recover after one attack and remain free from relapses. The figures give no support to the claims of greater effectiveness for either surgical or medical treatment, on the contrary they show that the results of the two methods leave little to choose between them.

The Effects of Chronic Irritations on the Morphology of the Peritoneal Mesothelium.—CUNNINGHAM (*Johns Hopkins Hosp. Bull.*, 1924, 35, 111) says that it has been found that the injection of laked or whole blood or any other mildly irritating substance into the peritoneal cavity, causes the serosal cells to increase in number and at the same time to round up, becoming at first cuboidal and finally columnar. When desquamation occurs, the remaining serosal cells proliferate rapidly and cover over the denuded area. The change may progress until the layer of mesothelium is several cells thick, and even in this state it is ample to prevent the development of adhesions. In long

continued irritations, connective tissue proliferation takes place and small outgrowths appear in the parenchymatous organs, but even here the changed mesothelium rapidly covers the advancing core of blood-vessels and connective-tissue stroma preventing the development of adhesions.

Diagnosis and Treatment of Syphilis.—KILDUFFE (*Am. Jour. Syph.*, 1924, 8, 142) states that diagnosis is essentially dependent upon the observation of certain phenomena in the patient, the recollection or knowledge that similar phenomena are associated with certain pathological entities and the correlation of the information thus obtained in terms of the patient. While it is admitted that the only venereal history of value is a positive one; nevertheless, careful history taking has produced many hidden but important leads. Stokes and Brown found that 70 per cent of syphilitics with gastric complaints had neuro-syphilis and what is of greater practical importance 60 per cent of their series had had no recognizable secondaries. Standard courses of treatment of all kinds abound in spite of the fact that there is and can be no true standard under all circumstances. The essence of the problem is perseverance and persistence, which alone spell safety. The so-called "Wassermann-fast" cases in the opinion of Stokes and Busman should not be dismissed from careful search for evidence of activity at intervals throughout life, for they are potentially syphilitic and show a high incidence of cardiovascular syphilis. These cases can be made negative by persistence and at times varied treatment.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,
NEW YORK.

The Action of Physostigmin and Pituitrin: The Action of These Drugs Alone and Combined upon the Isolated Human Vermiform Appendix; the Advantages of Their Combined Use in Postoperative Ileus.—KERR CROSS (*Brit. Med. Jour.*, January, 1924, p. 9) record the satisfactory results obtained by the subcutaneous injection of physostigmin, gr. $\frac{1}{160}$, and pituitrin, gr. $\frac{1}{2}$, for relief of dynamic ileus. Professor Gunn first pointed out the synergism between pituitrin and physostigmin from his work on laboratory animals, and this finding was confirmed by the author by his experiments on the human vermiform appendix. Neither drug alone produced much effect; but the drugs in combination caused a marked muscular contraction of the appendix. A number of cases of severe postoperative atony are described in which this combination relieved the condition when either drug alone failed to do so. No case treated has failed to be relieved unless there was unsuspected mechanical obstruction.

Addison's (Pernicious) Anemia and Subacute Combined Degeneration of the Spinal Cord.—In 1889 Hunter suggested for the first time that Addison's anemia is due to excessive destruction of blood caused by the absorption of hemolytic poisons from the alimentary tract. HURST (*Brit. Med. Jour.*, January, 1924, p. 93) believes that a definite infection of the intestine with a hemolytic streptococcus is present in Addison's anemia. In every one of the 10 cases of Addison's anemia and the 5 cases of subacute combined degeneration of the cord which were investigated the *Streptococcus longus* was found on cultivation of the duodenal contents. In normal individuals and in patients suffering from other conditions it was cultivated in only 10.9 per cent of cases. He believes that achlorhydria is an essential predisposing cause of Addison's anemia and its associated subacute combined degeneration of the cord because there is a loss of the normal antiseptic action of the gastric juice which makes it possible for the streptococci from the mouth to reach and infect the intestine. There is nothing specific about the achlorhydria, and it is in most cases caused by constitutional and congenital absence of gastric juice—achylia gastrica—in which no hydrochloric acid and very little or no pepsin are secreted, but it may also be caused by acquired achylia and by any condition in which such acid as is secreted is at once completely neutralized. The most important part of the treatment of these conditions consists in overcoming the intestinal infection and arresting the development of neurotoxic and hemolytic poisons. Oral sepsis should be eliminated, also infected tonsils, and infection of the sinuses corrected. The achlorhydria should be treated with large doses of dilute hydrochloric acid to each dram of which 1 gr. of pepsin is added. Six drams of dilute hydrochloric acid should be mixed with $1\frac{1}{2}$ pints of water to which sugar and the juice of three oranges or two oranges and one lemon are added. One-third of this amount is taken before and during meals. As the achlorhydria remains permanently in most cases this acid mixture should be taken for the rest of life without intermission. Milk which has been soured with an active lactic acid bacillus should be taken between meals in an attempt to check the growth of pathogenic bacteria in the intestine. Charcoal is also given in tablespoonful doses night and morning to absorb gas and correct flatulence. Autogenous hemolytic streptococcic vaccine made from bacteria obtained from the duodenum, teeth, or tonsils should be given over a long period of time and in doses so regulated as not to give rise to any general reaction. Splenectomy gave good results in 2 of his cases of anemia and by removing one source of blood destruction is a rational but not universally successful procedure. Symptomatic treatment should always be given, and arsenic and direct transfusion of blood are both of benefit. The latter may not only raise the percentage of hemoglobin, but frequently initiates a steady rise in the percentage.

The Principles of Treatment of Gastric Ulcer in View of Recent Work.—BOLTON (*Brit. Med. Jour.*, January, 1924, p. 139) states that the majority of gastric ulcers will heal if the normal responses of the stomach to the stimulus of food can be restored and maintained. He believes that the ulcer acts as an irritant and effects the neuromuscular mechanism of the stomach, the acidity of the gastric contents, and the

amount of gastric juice secreted. Irritability of the pyloric sphincter prevents normal relaxation and delay in the emptying of the stomach results. Because of the delay in the emptying of the stomach the percentage of free and combined HCl rises above the normal 0.2, at which point the pylorus should relax to allow regurgitation of bile and pancreatic juice. The result is that the HCl continues to rise, due to the prolongation of the digestive process which causes hypersecretion of the gastric juice. The treatment consists in an attempt to restore the normal gastric functions, that is, to lessen the neuromuscular irritability of the stomach and facilitate the emptying of the organ, and to restore the normal degree of duodenal regurgitation and to reduce the amount of gastric juice secreted. Preliminary treatment lasts six weeks, during which time the patient is put to bed to reduce expenditure of energy, the desire for food, and the work of the stomach. Gradually the diet is increased until the patient is eating the full diet to be allowed, and then he gets up and proceeds to the subsequent treatment, during which he eats the full diet he is to be allowed. At first the diet consists of the following foods presented in the following order: Milk, raw eggs, thin bread and butter, boiled eggs, cereals boiled in milk, pounded fish or chicken, mashed potato, sieved green vegetables, ordinary fish, chicken and mutton. Meat extracts are not given at all, nor meats nor other foods which are not easily disintegrated. Beginning with 7 ounces of milk every three hours from 7 A.M. to 10 P.M., the diet is gradually enlarged with substitution of the foods listed above, and eventually three meals a day are given. Alkalis are given one and a half to two hours after each meal and also once or twice during the night if the patient is awake. The best alkalis to administer are bismuth subcarbonate, calcium carbonate, magnesium oxide and soda bicarbonate. Atropin also has its uses particularly in relaxing the pyloric sphincter. The only direct means of dealing with a chronic ulcer is to excise it. Otherwise the aim of surgery is precisely the same as that of medicine, namely, (1) to facilitate the emptying of the stomach, and (2) to induce the regurgitation of intestinal fluids into the stomach. The writer believes that intestinal feeding should only be used in cases of bleeding from the stomach and in uncontrollable vomiting.

The Management of High Blood-pressure. — (*Therap. d. Gegenw.*, 1923, 12, 437) divides the cases of arterial hypertension into: (1) The acute arterial spasm with increased pressure; (2) the chronic hypertension, due to a hypertonic condition of the muscle cells of the arterial wall. The former are comparatively easy to influence, while the latter are very difficult. Baths, warm packs, light-baths, diathermy and also cutaneous irritants, such as the faradic current, may correct the former. Drugs which are effective are papaverin benzol compounds, such as benzol-benzoate and benzalcohol and particularly akineton, which is soluble in water and can be used intravenously in large doses. Papaverin, 0.08 gm., should be given in cases of arterial spasm. Spirits of camphor, 20 to 30 drops, often give good results; also extract of the anterior pituitary. The nitrites are also active, but their action, like many other substances becomes neutralized easily. Chloral hydrate also is an effective depressing agent, but in cases where the heart

muscle is good it often keeps up the effect of the irritating agent. The cases of chronic hypertension should be observed to determine their normal pressure, and the excess pressure corrected by means of vacations, rest, change of climate, avoidance of excitement, and avoidance of overweight. Diminution of salt intake in uncomplicated cases is of no benefit. Lukewarm baths and CO₂ baths are also of benefit. Drugs are useful in lowering the excess pressure only, but he also considers that it is important to give a diuretic weekly, or twice a week. Except in luetic cases he does not consider iodids of benefit, but often gives sodium rhodanate 1 to 3 gm. per day. He believed the dangers of permanent high blood-pressure are overestimated. The condition of varying pressure is serious, and the prognosis is unfavorable in those cases which show cerebral, renal or pancreatic symptoms.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Hypernephroma of the Ovary. Report of Case.—DOWNES and KNOX (*Jour. Am. Med. Assn.*, 1924, 82, 1315) report a case of this character of which only 11 cases are to be found in the literature. Only one of these other than the case herein reported began active growth in infancy and exerted the fundamental influences on growth and sexual development which such a tumor may do if active during the formative period of the individual. These 2 cases showed premature sexual development, a phenomenon that may result occasionally from disturbed ovarian function associated with a cyst or sarcoma of the gland, though it is by no means a constant finding with ovarian tumors in infants, as its frequent absence contributes to the difficulties of diagnosis. Suprarenal tumors composed of pigmented cortical cells arising in infants and in young children regularly cause striking developmental changes, while sarcoma and lymphosarcoma do not necessarily do so. In such a case as the one reported here, the effect is probably due more to the tumor cell type rather than to the secondary effects on the ovary, but it is impossible to separate these two factors completely, either normally or pathologically. Pure suprarenal types usually show a precocious growth of body and sex organs, overgrowth of hair and of fat, pigmentation and frequently mental dulness. Many patients have shown a tendency toward a masculine type. Precocious menstruation has only been noted once in the suprarenal group, and that was after the tenth year. Nearly all of these patients have died in childhood, either because of their glandular dyscrasia has rendered them very susceptible to intercurrent infections, or more often because the tumors, being large, inaccessible and frequently metastasizing at the time of operation, have caused the patient to succumb at the time of the

operation. The ovarian cases, with readily accessible benign growths have been frequently greatly improved by operation, and a recession of the pathological characters has occurred. The interrelation of the endocrine glands is undoubtedly very important, most of the symptoms are due to imbalance of the secretions.

Congenital Mitral Stenosis.—DONNALLY (*Jour. Am. Med. Assn.*, 1924, 82, 1318) reports a case that died at the end of fifty-seven hours. This is the twelfth case in the literature in which autopsy findings definitely established the diagnosis. He says that the explanation of this anomaly is comparatively simple. The defect happened during the differentiation of the mitral valve out of the endocardial cushions. The free margin of these cushions grow down into the ventricles, and the muscular trabeculae from the heart walls invade their structure, and form their attachments so that for a time the valve consists partly of endothelial growths and partly of musculature. A differentiation into muscoli papillares, chordae tendinae and valve flaps develops as the musculature in these structures degenerates. This is the point at which something happens in congenital stenosis to prevent the normal development into valve segments. Growth is arrested in the mitral valve and in those chambers and vessels whose growth is dependent on the proper functioning of the left auriculoventricular orifice, particularly the left ventricle, aorta and left auricle. The completion of the subdivision of the heart, the almost complete development of the valve apparatus, and the outer form of the heart occur by the time the embryo is eight weeks old. With the establishment of the narrowed left auriculoventricular passage, arrest in development of the left heart ensues because of the small amount of blood that is permitted to take the normal through it, while there is dilatation and hypertrophy of the right heart because of the amount of blood that it receives and propels. As the intraventricular septum was completely formed and closed in this case, blood entered the left ventricle solely through the stenosed mitral orifice, but in such small volume that this ventricle had almost no function to perform and remained undeveloped. The left auricle, receiving the blood from the lungs and unable to send it into the left ventricle, may have passed it through the foramen ovale into the right auricle. It is difficult to say that this was definitely the case, although the large and comparatively powerful right ventricle may have made its force felt through the pulmonary circulation and have been an added factor to left auricular contraction to produce this result. In the literature, the children with the greatest duration of life showed a closed foramen ovale. This indicates that patency of the foramen ovale is not of great compensatory value. In this case almost the entire function of the heart was performed by the right side. As a result, there was an enlarged right ventricle and dilated pulmonary artery. Persistence of the ductus arteriosus permitted the passage of blood through the aorta in a reverse to the normal direction into the vessels of the head and upper extremities and onward into the thoracic aorta.

Wilson's Disease in Infancy.—PAUL (*Arch. f. Kinderh.*, 1924, 74, 38) reports a case of an infant with tonic spasm, jaundice, normal color of feces, and much enlarged liver, but absolutely normal spleen. He

diagnosed this as Wilson's disease, which is an extrapyramidal symptom-complex, concomitant liver cirrhosis and lenticular degeneration. Banti's and Gaucher's disease and syphilis could be positively excluded. Since the pallidum symptoms harmonized with the second type of Little's disease, the case might be diagnosed as Little's disease as well. Along with the typical pallidum symptoms, dorsal flexion of the foot, crossing of the legs, flexion of the knees, dropping position of the hands, increased surface tonicity of the muscles and non-decreasing muscle rigor during passive motions there occurred one striatal symptom, opisthotonos.

Further Notes on the Treatment of Pertussis by the Roentgen-Ray.
—BOWDITCH (*Jour. Am. Med. Assn.*, 1924, 82, 1422) presents the results of treating 300 cases of pertussis by the roentgen-ray. Patients were given treatments every alternate day for three treatments. After an interval of seven days, a similar second course of treatments was given in the more protracted and resistant cases. These additional treatments were infrequent, as they did not as a rule seem necessary. The ordinary dosage for a child of from five to ten years was five minutes exposure with the tube set at 4 ma.; a 1 mm. aluminum filter and a 6- to 7-inch back-up-spark at a distance of 28 inches, was employed. This dosage was gradually graded down somewhat, according to the age of the patient, so that an infant of three or four months would receive the same dosage, with the exception of the time interval which would be three instead of five minutes. The first treatment was given over the anterior chest, the second over the back of the chest, and the remaining treatments alternating in this manner, the total dosage was well within the limits of safety, four exposures totaling less than one-half an erythema dose. In case the symptoms persisted a second series of treatments of the same dosage was given after an interval of ten days to two weeks. This happened rarely. Very few of the patients had more than four treatments. The clinical course of the disease seemed to be definitely modified. Within a few hours after the first treatment, the patient experienced a feeling of relief. The symptoms were reduced in severity and duration. At the end of twenty-four hours, the symptoms usually reverted to their former degree, and the next day no very marked effects of the treatment was noted. After the second treatment, the symptoms usually fell back a little. There were some cases in which the severity of the paroxysms was less after the first treatment. The most marked changes followed the third treatment. The patient seemed more noticeably relieved as the severity of the paroxysm was reduced, whooping almost disappeared, cyanosis and vomiting became minor factors, and often more uninterrupted sleep at night followed. By the end of the week, the appetite usually improved, and the patient was much better. While these results do not always follow, in general the earlier the case is treated, and the younger the patient the better is the response. Extremes were encountered. Sometime the mother reported a cure as the result of one treatment. Other cases persisted with no very marked benefit in spite of the two courses of treatments. In the entire series of cases, including 100 children under two years of age, only 1 death occurred.

Meningitis: Distribution According to Age and Etiology.—NEAL (*Jour. Am. Med. Assn.*, 1924, 82, 1429) analyses 1523 cases. She found that with the exception of tuberculous meningitis more cases of meningitis occur in the first year of life than in any other one year. The number of cases of meningococcic meningitis in the first year exceeds by far those in any other year. The greatest number of cases of tuberculous meningitis is found in the second year of life. In times when there is no epidemic, the number of cases of tuberculous meningitis exceeds or at least equals the number of cases of meningococcic meningitis. After the meningococcus, the pneumococcus and the streptococcus are the most common causes of purulent meningitis, followed by the influenza bacillus, the staphylococcus and *Bacillus coli* group, in the order named. Cases due to the last two organisms are comparatively rare. Other pyogenic organisms occasionally cause a meningitis, and more rarely, members of the higher group of organisms such as members of the streptothrix and the pathogenic yeasts are the causes. Mixed infections are rare.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

MAYO CLINIC, ROCHESTER, MINN.

The Pathogenesis of Arsphenamin Death.—KRITSCHESKY (*Arch. f. Dermat. u. Syph.*, 1923, 144, 32, 47) and KRITSCHESKY and FRIEDE (*Ibid.*, p. 61) discuss at some length in connection with experimental studies the pathogenesis of arsphenamin death. In his introduction, Kritschewsky calls attention to the arsphenamin mortality of 16 per 100,000 in the German empire from 1909 to 1914, and the fact that this mortality would reach 514 per 100,000—5 per 1000 patients—if the accidents indirectly attributable to arsphenamin were included. He reviews in some detail the various conceptions of acute arsphenamin death, including the conceptions of water-error from the endotoxins of bacterial contamination, Herxheimer flare-up in secondary syphilis, the anaphylactoid manifestations of nitritoid crisis, and the later complications including especially the cerebral manifestations of hemorrhagic encephalitis. He includes in this group several cases with prolonged "incubation periods" ranging from six weeks to three months, which must seem somewhat apocryphal to us. Kritschewsky employed in his investigation the determination of the effect of injected arsphenamin solutions upon the complement content of guinea-pig serum as an evidence of changes in its colloidal dispersion following the administration of the drug. This method has been made the subject of previous study by this author and was regarded as a reliable index to colloidal change. He found that *in vitro* definite reduction or fixation of complement occurred following the administration of arsphenamin

as indicated by a hemolytic system. This physico-chemical change took place although no visible precipitate appeared in the blood serum such as is known to form with acid arsphenamin. He then transferred his experiments to animals and demonstrated that similar changes occurred in the rabbit and mouse indicating an alteration in the dispersion of the serum even by properly alkalized arsphenamin solution. The effects of this physical change were manifested in the occurrence of intravascular coagulation with agglutination of red blood cells which in accord with observations of Oliver and his co-workers previously reviewed. Kritschewsky believes that the mechanism by which this colloidal dispersion is produced is identical with that producing the dispersion changes of anaphylactic shock. In this respect he differs with the views of certain American investigators who do not believe that acute arsphenamin intoxication should be regarded as anaphylactic in character. In collaboration with Friede, Kritschewsky carried his experiments further, studying the pathological changes produced by acute arsphenamin death. These confirm in large measure the findings of previous investigators with reference to the role of wholesale intravascular thrombus formation. The tremendous pathological change occurring in the tissues is of the type which one would expect with disturbance of their colloidal equilibrium, including liquefaction of muscle tissue and confirms his opinion that colloidal changes form the ultimate basis of the damage done by arsphenamin to tissue. In further experimental studies he was able to demonstrate the neutralizing or buffering power of serum against toxic arsphenamin; results which are also in accord with the work of Oliver and his collaborators on colloid (gelatin) buffering of arsphenamin solution. Kritschewsky finds in agreement with Gennerich and other authors that the concentration of the arsphenamin solution is one of the most potent factors in determining its effect upon the body colloids and the toxic reactions which it produces. Arsphenamin given in high concentration is much more dangerous than when well diluted.

Familial Dermatositis.—THOMPSON (*Brit. Jour. Dermat. and Syph.*, December, 1923, p. 455) describes a familial dermatosis of which he has been unable to find any account in the literature. Two girls in the same family were affected. The older child developed the condition at the age of one month in the form of a small red patch appearing on the most prominent part of each buttock. Similar lesions then developed in the face and gradually extended until both cheeks were greatly swollen, tense and highly polished and of a vermilion color. There was considerable underlying cyanosis and the hands were cyanosed and swollen though the feet were unaffected. Both buttocks showed changes similar to the cheeks. Marked improvement occurred under small doses of thyroid. The swelling and some of the color disappeared but a telangiectatic and nevoid condition persisted. At last report the process was extending steadily over the forearms and the extensor surfaces of the legs. The condition showed a predilection for the extensor surfaces. In the gross, the condition suggested greatly exaggerated *cutis marmorata*. The child was very susceptible to cold and the skin becomes purple at these times. The younger child was beginning to present the same manifestations as the older. Investigation

for syphilis so far as the Wassermann test is concerned was negative. The condition of the older child has persisted now for two years and the skin of the younger is just beginning to be affected at the age of three and a half months. At their very onset, the lesions were apparently follicular and had a nutmeg-grater feel. In the discussion erythroedema (pink disease) and angioma serpiginosum were considered but were apparently eliminated from the diagnosis. There were no systemic phenomena to suggest erythroedema. The same issue of the *British Journal of Dermatology and Syphilis* contains an excellent review from the *Medical Journal of Australia* of an article by E. Sidney Littlejohn, summarizing the symptomology of erythroedema or "pink disease."

Spinal Fluid in Syphilitics without Manifestations of Neurosyphilis.—M. PAPPENHEIM (Vienna) (*Arch. f. Dermat. u. Syph.*, 1923, 144, 117) discusses the significance of the spinal fluid in patients with syphilis who show no manifestations of neurosyphilitic involvement. As a result of an extended review of the literature, he reaches the following very interesting conclusions: Increased pressure of the spinal fluid is without significance with reference to involvement of the nervous system in syphilis; isolated increases in albumen (positive globulin tests) are likewise not of unfavorable prognostic significance; syphilitic patients who in the stage of advanced latency show marked abnormalities in the spinal fluid may be regarded as proportionately seriously in danger of neurosyphilitic involvement. On the other hand, it is noteworthy that a considerable number presenting even severe changes do not later develop neurosyphilis. The immunity of women in this particular is pronounced. Statistical studies by Fuchs and Meyerbach make it seem very probable that not a few syphilitic patients in advanced latency have normal spinal fluids but none the less develop neurosyphilis. Pappenheim opposes the belief that later neurosyphilis is practically always the sequel of an early syphilitic meningitis. The changes in the spinal fluid in certain cases in advanced latency may be regarded as the sequels of parenchymatous involvement rather than its predecessors.

Cutaneous Sporotrichosis in the Rat.—JESSNER (*Arch. f. Dermat. u. Syph.*, 1913, 144, 139). The author finds that cutaneous sporotrichosis in the rat because of its uniform incubation period and relatively long intervals between the disappearance of the traumatic inoculation crust and the beginning of manifestations of the disease, lends itself particularly well to the study of immunity of phenomena. The histological picture is very typical and consists of a connective-tissue reaction developing in the course of the existing immunity and expressing in a definite way the course of the developing immunity. Immunity reaction against cutaneous reinfection begins before the clinical manifestations of the first infection develop. The incubation period does not, therefore, represent as required by the von Pirquet and Schick theory, merely the time from inoculation to the beginning of the disease. It is necessary, therefore to distinguish in certain infectious diseases especially of the skin, as Neisser suggested in the case of syphilis, between a clinical and a biological incubation period. The latter is defined as

the time between the introduction of the exciting agent and the appearance of any detectable evidence of defense. The immunity incubation time is the period from the introduction of the exciting agent to the appearance of immunity against reinfection of the same agent. In sporotrichosis in rats the immunity incubation is shorter than the clinical incubation. The immunity against cutaneous infection appears later when the initial infection is subcutaneous than when it is cutaneous. The allergic response to subcutaneous reinfection is, in both subcutaneous and cutaneous initial infection, more pronounced at the site of previous inoculation than in sites not previously involved. This is of significance in the corymbose lesions of late syphilis and leishmaniosis in which the site of a previous involvement shows a markedly greater sensitiveness than previously uninvolved tissue. Jessner found evidence that tuberculoid histological structure is an allergic tissue reaction and appears at points where the infectious agent is being broken down under the influence of antibodies.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

A Clinical Study in Hydrops Gravidarum.—SCHOEMAKER (*Arch. f. Gynäk.*, 1923, 119, 305) has made a study of this condition, and finds that at the end of pregnancy 64 per cent of women show some sign of edema if the examination be made in the morning hours, and at evening 95 per cent of these same patients show edema in varying degree, and the lower extremities are markedly swollen in 11 per cent. In 200 pregnant patients general edema without pathological changes in the urine was observed only twice. In 3 per cent of the cases both morning and evening examination of pregnant women showed no edema. A slight edema at evening in pregnant women is without significance and does not prove that water is retained in the body because of pregnancy, because the same condition is observed in healthy women who are not pregnant. Marked edema is significant in the pregnant when it is attended by irregularity in weight and when in the puerperal period there is great increase in diuresis with also gain in weight above the normal. In general, in the last month of pregnancy 73 per cent of pregnant women show edema to some extent; this usually begins in the thirty-fourth week and becomes more marked as pregnancy advances. Swelling of the fingers is comparatively rare, occurring in 15 per cent of the cases, and usually denotes a marked pathological condition. When the diuresis of pregnant women is studied no marked difference can be detected between that of the night and that of the day. The concentration test is successful and significant in cases of edema of pregnancy and indicates that the

function of the kidneys is not especially disturbed. The rest nitrogen is below the normal in the urine in the most severe forms of edema. Blood-pressure is not, as a rule, altered in the mild forms of edema. Actual changes in the structure of the heart cannot in these cases be demonstrated. The fact that edema does not depend upon conditions in the kidneys suggests that in treatment rest in bed, diet free from salt and with a limited quantity of water is indicated. Where the condition is severe free sweating may be of service.

The Significance of Jaundice in Eclamptic Cases.—OPPENHEIMER (*Monatschr. f. Geburtsh. u. Gynäk.*, 1923, 5, 289) describes the case of a primipara, aged nineteen years, with typical eclampsia; blood-pressure, 150; albumin and granular and hyaline casts in the urine. The patient was at once treated with narcotics by Stroganoff's method, including the use of chloroform. Delivery was effected by incising the partly dilated cervix and using forceps; the child was somewhat premature and to some degree asphyxiated. In the two days following labor the temperature rose to 102.5° F.; pulse, 150; there was cyanosis and dyspnea, and on the third day marked jaundice was present and the conjunctivæ were deeply colored. In the urine was biliary coloring matter and urobilinogen. Eclamptic convulsions recurred; Stroganoff's treatment of bleeding, injecting glucose and using chloroform, was continued. In addition to the jaundice there appeared reddened areas on the face, forehead, cheeks and upper portion of the thighs, which was diagnosed as toxic erythema. This gradually disappeared; three days later the temperature again rose and petechia developed; from this the patient became better and, after some disturbance in the stomach, she finally recovered. During this time the rest nitrogen in the blood was never increased nor was blood sugar. In the urine the albuminoid content was lessened and rapidly became less; casts disappeared, but urobilin and bilirubin and urobilinogen were present and diazo reaction could be obtained. Various tests for bilirubin in serum gave a marked increase without an especially increased diazo reaction. The leukocytes rose to 30,000; the hemoglobin was somewhat lessened followed by a rapid fall in the number of leukocytes and increase in hemoglobin. An acute toxemia developed in the first stage of labor, and it is interesting to note that convulsions returned three days after the delivery of the child. Such an occurrence is rare, but Olshausen has reported a case where convulsion reappeared seven days after labor in an eclamptic woman. The history of the patient gave no evidence of previous disease or infection of the liver, gall-bladder or intestines. There was no history of poisoning by phosphorus or arsenic. Wassermann reaction was negative; examination of the blood for typhoid and paratyphoid was also negative. It was thought that the clinical picture was that of acute yellow atrophy of the liver; in that condition icterus appears at the very beginning or very early in the attack. In the case under consideration no diminution in the size of the liver could be detected; the writer considered the action of chloroform upon the liver and also that of chloral hydrate; before the appearance of the jaundice chloroform had been used for a considerable time, and the patient had been given 6.5 gm. of chloral

hydrate. On studying the clinical records it was found that jaundice may develop in cases where chloroform and chloral hydrate are not used; upon this ground the writer believes that these substances were not the cause of the jaundice. The writer believes that van den Bergh's method of estimating the bilirubin in the blood gives excellent grounds for estimating the gravity of the condition present in these cases. The prognosis in these patients is usually exceedingly bad; in the writer's experience in cases of icterus complicating eclampsia the mortality was 14.3 per cent, and if 6 very mild cases are removed from the category the mortality rises to 22 per cent. The mortality rate for eclampsia without icterus, he states, was 19.7 per cent. He is disposed then to revise the usual opinion that icterus developing in the course of eclampsia is not exceedingly deadly—an opinion which is very natural in a physician who has had a case followed by recovery.

The Post-mature Child.—O'KEEFE (*Am. Jour. Obst.*, November, 1923, p. 388) describes the difficulties seen in the delivery of post-mature children. There is a higher percentage of injuries to the mothers and higher mortality and morbidity among infants. The occiput was posterior more frequently than normal and rotates less readily spontaneously or by artificial means. There is greater difficulty in selecting the method of delivery, and the delivery itself is often difficult. The cause for the prolongation of pregnancy is not definitely known and in some instances it would seem as if the unusual growth of the child had something to do with it. There were 152 cases of children weighing 4000 gm. or more; of these 148 were white and 4 negroes. There were 144 pelves classified as normal, the others contracted or deformed. It is difficult to obtain an accurate menstrual history in these cases and, from the history itself, to compute accurately the intrauterine life of the child. There were 151 vertex presentations and 1 breech. Of the vertex presentations 31 had the occiput on the right side posteriorly, of which only 27 rotated spontaneously. There were 17 cases with occiput behind on the left side and of these 14 rotated spontaneously. The tendency to posterior position of the occiput increased directly with the weight of the child. The average length of labor was thirteen hours and nineteen minutes. In 82 cases morphin and scopolamin were used; pituitrin was given in 42 cases, varying from an injection of 1 M. to eleven injections averaging each 4 M. In 1 of these cases that had the largest number of pituitrin injections before birth the uterus relaxed immediately after delivery, and it was difficult to control the hemorrhage. Forty-one of the children breathed spontaneously; of these 1 died on the third day from pneumonia, another from intracranial birth injury. Labor had been induced in these cases, in the first with pituitrin alone and in the second with pituitrin and bougies. There were 5 abnormalities among these children; 5 injuries and 5 still-births. The 10 fatalities among the children gave an infant mortality of 6.5 per cent. The average weight was 4262.6 gm.; length 51.96 cm., with measurements corresponding. The writer considers the question of treatment by diet and the induction of labor.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, MEDICAL SCHOOL, UNIVERSITY
OF PENNSYLVANIA, PHILADELPHIA.

Indications for Myomectomy.—In recent years myomectomy seems to be regaining its old popularity in the treatment of certain types of uterine fibroids, and we have from time to time called attention to reports of fairly large series. Although the series reported by MILLER (*New Orleans Med. and Surg. Jour.*, 1924, 76, 355) is not very large, it is carefully analyzed and may be of value to those interested in this subject. In 50 consecutive cases there was 1 fatality, a 2 per cent mortality, and of the 35 cases which he was able to follow up, there was only 1 recurrence (2.8 per cent). Following the operation 95 per cent of the patients menstruated normally and 97 per cent of the cases report their general health markedly improved. Five per cent of the patients report menstruation still profuse, though in practically all of the cases the flow is distinctly less. Dysmenorrhea is very commonly associated with fibroids, and a large number report this symptom either improved or more readily controlled by simple measures. Two patients have not menstruated since the operation; one of these was forty-eight years of age, and the myomectomy was done in the course of very extensive work in the upper abdomen; the other patient was thirty-six years of age. The conclusion to be drawn is that about 5 per cent of the cases will continue to menstruate profusely following myomectomy. Nevertheless, since we have an ideal therapeutic agent in radium, which can be used in graduated doses without producing a premature menopause, this objection is also not insuperable. The next important point to be considered is what percentage of women bear children after this operation. So many considerations enter into this however, that no definite conclusions could be drawn without an exhaustive study of a large series of cases. In this series, among the 35 patients who were followed, 6 were unmarried, and there were 10 pregnancies among the remaining 29 patients (about 28.6 per cent). Of these, 6 patients (60 per cent), had not been pregnant previously. Of the 19 who had the chance of pregnancy and did not conceive, it is interesting to note that 14, or over 75 per cent had been married prior to the operation sufficiently long to have borne children, and yet had never been pregnant. The average woman desires to preserve the menstrual function and to become pregnant if she can, and myomectomy makes both of these things possible, while pregnancy follows in a sufficient number of cases to recommend the operation unqualifiedly whenever it is indicated. Some women will insist upon the assurance that hysterectomy gives, that there will

be no return of the trouble, and request that that type of operation be done which will make the outcome final. However, if the advantages of myomectomy are placed before the average woman, and if the possibility of the use of radium if the trouble does recur is explained to her, she will usually prefer myomectomy when it can be performed. In deciding whether hysterectomy, myomectomy or radium is indicated in uterine fibroids, we must taken into consideration not only the number, size and location of the fibroids, but also the age, social and financial condition of the patient. When a woman is dependent on her own efforts, and perhaps is supporting a family also, when it is imperative that she return to work at the earliest possible moment and in the best possible condition, no chance must be taken of a second operation or even further treatment. Myomectomy has few indications after the age of thirty-eight, and in this series 86 per cent of the cases were under this age. When a woman has several living children there is less reason to preserve the uterus than in the case of the woman with no children who particularly desires motherhood. It is well to preserve the uterus if possible when there is an associated prolapse, as an interposition operation can be done with satisfactory results and with no danger of a subsequent prolapse of the vaginal walls. Neither radium nor myomectomy have the slightest indication when there is associated disease of the appendages. In brief, the ideal case for myomectomy is the single, well-defined encapsulated tumor. As a rule, the case presenting numerous small growths does not give satisfactory results. It is easy to overlook them, and if they are of different types and widely distributed, a damaged and useless organ may be left and the whole point of the operation be defeated. The author has, however, removed as many as 18 growths from one uterus, the woman afterward conceiving and delivering normally, and in 28 of the 50 cases in this series multiple growths were removed, some of them from five to eight inches in diameter.

Gonorrheal Complement-fixation Test in Women.—As a result of their work with the complement-fixation test in the diagnosis of many women afflicted with gonorrhea, most of whom were prostitutes, BARRINGER and VON BOSE (*N. Y. State Jour. Med.*, 1924, 24, 10) have concluded that they are willing to make a definite diagnosis of gonorrhea on a "plus or minus" reaction, which they consider a weakly positive reaction, as they are satisfied that a non-gonorrheic does not give a positive reaction. In women the test has a distinct value, which is greatest in the chronic and subacute cases, from the standpoint of diagnosis and prognosis. It is of less value in acute cases, from the standpoint of diagnosis, but probably of equal value from the standpoint of prognosis. This study has proven the subsidence of the complement-fixation reaction along with the clinical symptoms, while the reappearance of a high complement-fixation reaction during convalescence suggests an active focus. A persistently negative complement-fixation reaction with positive bacteriological findings is rare and cannot be satisfactorily explained by these observers, but a persistently negative test with negative clinical and bacteriological findings can be interpreted as an index of the probability of a cure of gonorrhea in women. It is always a difficult matter to state just when a woman has been

cured of gonorrhea but these investigators suggest as a tentative and entirely standard that, in order to pronounce a cure, it is necessary to have three persistent negative findings over a period of six months. They fix this arbitrary time as they believe the cure in women is probably somewhat slower than in men.

Operation for Uterine Prolapse.—In describing his new operation for uterine prolapse, GILL (*Med. Jour. Australia*, 1924, 1, 37) claims that it is suitable for use in all forms of extreme prolapse in women past the child-bearing period, provided that the uterus be healthy enough to be preserved and irrespective of the size of the organ. The abdomen is opened in the midline, the uterus drawn out and the tubes and ovarian vessels are clamped, divided and tied. The broad ligaments are opened by blunt dissection and the uterine arteries are picked up and tied. The uterus is then replaced in the abdomen with the anterior surface exposed. From this surface two flaps 4.25 cm. long and 2.5 cm. wide and 0.6 cm. thick are raised, the attachment along their mesial borders being retained. The uterine cavity is not opened. While the flaps are protruding through the wound the peritoneum and aponeurosis are closed by continuous sutures of catgut around the flaps. The uterine flaps are then laid flat on the aponeurosis and sutured to it by interrupted sutures of catgut. In spite of ligating both ovarian and uterine arteries the flaps remain well nourished, yet there is no troublesome hemorrhage from the beds from which they are raised. As with every other operation for prolapse, a thorough repair of the pelvic floor is essential.

Stricture of Female Urethra.—Although stricture of the female urethra is often looked upon as a rare condition, PUGH (*Ann. Surg.*, 1924, 79, 770) found this condition in varying degree in 35 of 180 women presenting urological symptoms and therefore he calls the condition common. In this series the causative factor was gonorrhea in 24, chancroid 2, syphilis 1, childbirth trauma 1, keloid 1, possible focal infection 5. As this list shows, gonorrhea is probably the main factor in stricture of the urethra. In most cases frequency and dysuria are the symptoms most commonly complained of, and in several the symptoms more strongly suggested abdominal and renal lesions than they did urethral. Many cases present most remote symptoms, and if one is not careful, he may think the patients are neurotic. The retention of urine by women for long periods is so common that they often seem to think it a natural condition. Far more do women complain of dribbling (really an incontinence of retention) than they do of obstructive symptoms. Slight obstruction however, is often sufficient to produce a marked cystitis and urinary changes. Pugh states that we must not look for the classical text-book symptoms in urethral stricture in women, as it is unusual to find them. If, however, we take a careful history and find any suggestive urinary symptoms, we are justified in making a urethral examination. In fact, we should do it as a routine in all our female urological cases, using for the purpose either the olive tipped bougie or the bulb. The location of the stricture in this series was at the external meatus in 18, anterior third 12, middle third 1, posterior third 4. The prognosis depends largely on the etiological factor.

Soft infiltrations usually respond well to treatment, while the hard infiltrations are always a source of doubt as to their ultimate cure. In dilating these cases it is always best to begin the dilatation with the largest sound or bougie that will pass the stricture and then increase two numbers a week, until we reach the normal urethral caliber, which is about 26 F. After this, the large dilator should be passed once a month for a year, and even after that it will be wise to examine the patient every six months for evidence of return. In the hard infiltrations, the treatment must be more cautious than it is in the soft, as laceration of the urethra readily occurs. In cases of impassable stricture and even in some filiform strictures, it may be necessary to do a urethrotomy, which should be an internal urethrotomy if possible.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO; TORONTO, CANADA,

AND

DE WAYNE G. RICHEY, B.S., M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY, UNIVERSITY OF PITTSBURGH; PITTSBURGH, PA.

The Effect of Loss of Sleep on the Composition of the Blood and Urine.—RAKESTRAW and WHITTIER (*Proc. Soc. Exper. Biol. and Med.* 1923, 21, 5) conducted a series of experiments on 8 normal men, on a uniform diet, who remained awake over a period of forty-eight hours. Twenty-four-hour urine samples were collected for two days of the wakeful period, as well as the normal day preceding. Blood samples were taken at the beginning, middle and end of the period. The whole experiment was repeated after an interval of three weeks, the men alternating as controls and subjects in the two periods. Total nitrogen, urea, ammonia, chlorides, phosphates, uric acid and total acidity were determined in the urine by the customary methods; while in the blood, determinations were made of sugar, non-protein nitrogen, urea, phenols, uric acid, chlorides and alkali reserve. In 4 cases total "acid soluble" phosphorus and lactic acid were also determined in the blood. The results showed no really consistent alteration in any of the components studied with the exception of a possible increasing tendency of the total nitrogen and the phosphorus of the urine and an increase in the lactic acid and phosphorus of the blood. The data concerning these last two components were too fragmentary to justify any positive conclusion. No considerable alteration in the composition of human blood or urine was produced by the forty-eight-hour loss of sleep.

A Note on the Antigenic Properties of the Filtrate of Typhoid Saline Vaccine.—Inasmuch as PERLZWEIG and STEFFEN (*Jour. Exper. Med.*,

1923, 38, 163) have shown that the immunizing antigen of the pneumococcus may be extracted from the bacterial cells by 70 per cent alcohol, physiological salt solution, and by water and that the supernatant fluid of old pneumococcus saline vaccines when filtered through a Berkefeld candle conferred active immunity upon mice after several subcutaneous injections, PERLZWEIG, WELLS and AMOSS (*Proc. Soc. Exper. Biol. and Med.*, 1923, 21, 28) conducted a series of experiments on the antigenic properties of the supernatant fluids of other vaccines. Two rabbits were injected intravenously with successive doses of a triple typhoid saline vaccine and two with a Berkefeld (N) candle filtrate of the supernatant fluid of the same vaccine. The determinations of the agglutinin and precipitin titers of the rabbit sera indicated that it was possible to obtain in the sera of rabbits with the filtrate almost as high a titer as in the sera of rabbits treated with the whole vaccine. Their results showed that at least two of the antigens, the agglutigen and precipitinogen, of the typhoid bacillus are soluble in and can be extracted by dilute salt solution. The authors state that "that these antigens are in all probability distinct from the higher protein constituents of the bacterial cell may be deduced by the heating of the vaccine in the process of manufacture and also by the fact that the supernatant filtrate used in this experiment gave a barely perceptible biuret reaction . . ."

Protection Against Typhoid-like Infections by Vaccinations. An Experimental Study.—"The basic fact that infections with the typhoid bacillus can be prevented by vaccination is, of course, well established by clinical evidence. It is also supported, theoretically, by a certain amount of experimental evidence. The experimental solution of these problems has been delayed by the impossibility of reproducing a true typhoid infection in the common laboratory animals. In the absence of a real protection test, efforts have been made to settle many questions by a quantitative determination of the antibody content of the serum of vaccinated animals. This method has been of practical value in some directions, but of course, in general, is inferior to an actual protection test." NICHOLS and STIMMEL (*Jour. Exper. Med.*, 1923, 38, 283) took advantage of a spontaneous and severe epidemic among guinea-pigs, which furnished them with a picture of the natural disease, to ascertain the efficacy of a vaccine, using the causative organism, which was the "mutton" strain of *B. aertrycke*. Male guinea-pigs were inoculated, subcutaneously, at eight- to ten-day intervals and fifteen days after the last dose of vaccine were given the infecting dose of *B. aertrycke*; also subcutaneously. In each experiment, as far as possible, four animals were used, with four normal controls, and four controls vaccinated with fresh, full strength, saline vaccine, 1 cc of which contained about 1000 million organisms. Careful bacterial examinations of the blood, spleen, liver and gall-bladder were made on all animals that died. Under the conditions of the experiment, it was found that complete protection was secured by vaccination with full strength fresh saline vaccine, while 100 per cent of deaths occurred among the controls. The immunity acquired was variable and depended on the number of organisms injected. Vaccine kept ten to fourteen months gave less protection than vaccine eight months old and under.

Saline vaccine was more effective than lipovaccine, sensitized vaccine, or supernatant fluid vaccine. Resuspended vaccine was as effective as the original vaccine. In one experiment, group vaccine, made of typhoid Para A and Para B bacilli, was as effective as the original specific vaccine.

Serological Agglutination of *Bacillus Sporogenes*.—"The success of MEYER (*Jour. Infect. Dis.*, 1915, 17, 458) in differentiating *Vibrio septique*, *B. chauvoei* and '*B. oedematis maligni*' (*B. sporogenes*), and in identifying *Vibrio septique* by the agglutination test," led HALL and STARK (*Jour. Infect. Dis.*, 1923, 33, 240) to use this method in differentiating and identifying certain pure cultures which had been unnamed. This procedure resulted in the segregation of 19 cultures which were later identified as *B. sporogenes* by their morphological and cultural characteristics. Marked differences in the titer of a given serum occurred when tested on different strains of this species, some strains of *B. sporogenes* failing to agglutinate even at 1 to 20. On the other hand, none of the *sporogenes* serums ever gave a positive test with any other species, nor did any serum prepared against another species ever agglutinate a strain of *B. sporogenes*. Consequently, the authors regarded "serological agglutination as a satisfactory criterion of species identity in properly controlled positive tests, but not of differentiation in negative tests." Immune serum was prepared by injecting a rabbit subcutaneously, with a forty-eight-hour glucose broth culture of *B. sporogenes* in 6 doses of 1 to 3 cc at intervals of two to three days during a period of two weeks. Following a rest of three weeks, 5 cc of blood were drawn from the ear and a slightly positive result was obtained at a dilution of 1 to 20. Subsequent injections increased the titer, the serum being active in a dilution of 1 to 1000. The agglutination tests were carried out at 37° C, using twenty-four or forty-eight-hour glucose broth cultures and readings were made after two hours' incubation. The authors conclude that agglutinating serums of high potency for *B. sporogenes* can be prepared easily by intravenous or subcutaneous injection of rabbits with glucose broth cultures; that these serums are specific for *B. sporogenes* and do not agglutinate other species; that there was a tendency toward strain specificity, more marked in some strains than others; that positive tests properly controlled identify, but negative tests may not differentiate some members of this species, except antigenically, and that sera from several other species of obligate anaërobes failed to agglutinate *B. sporogenes*.

The Study of Hemolytic Streptococci Associated with Scarlet Fever.—With the object of studying the agglutination of streptococci from the throats of patients with scarlet fever and the phenomenon of agglutinin absorption with these bacteria, STEVENS and DOCHEZ (*Proc. Soc. Exper. Biol. and Med.*, 1923, 21, 39) collected strains from cases of scarlet fever occurring in several large cities of the United States and in Copenhagen, Denmark. From the throat cultures of 40 acute cases, hemolytic streptococci were isolated in 87.5 per cent, of which 74.3 per cent were agglutinated by immune sera prepared with two scarlatinal strains. Among the convalescents streptococci were found in 47.3 per cent and 55 per cent of these strains could be agglutinated with

scarlet immune sera. When strains obtained from a milk borne epidemic of scarlet fever and those obtained from scarlet fever occurring in the cities were examined for cross agglutination, it was found that, in the main, the cross agglutinations were consistent, and strains obtained from conditions other than scarlet fever were not agglutinated. In the absorption tests, which were performed at 55° C., fresh immune sera and strongly agglutinable strains were necessary for agglutinin absorption. All the combinations of sera and strains did not give absorption but each strain was represented in the absorption experiments, since absorption of agglutinin from several immune sera was accomplished with each strain or immune serum prepared with a given strain was absorbed by several other scarlet strains. The authors conclude that the strains of hemolytic streptococci associated with scarlet fever are closely related biologically, and probably constitute a single unit group.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

Studies on the Relation of Mineral Dusts to Tuberculosis: III. The Relatively Early Lesions in Experimental Pneumokoniosis Produced by Carborundum Inhalation and Their Influence on Pulmonary Tuberculosis.—GARDNER (*Am. Rev. Tuberc.*, 1923, 7, 344) reports the results of his study of the effect of carborundum dust upon the normal and the tuberculous guinea-pig. He states that certain factors in the biological reaction of the normal and of the tuberculous animal to this irritant have been established. When this dust is inhaled it is widely distributed throughout the parenchyma of the lung. Once deposited, it tends to remain *in situ* but there is a tendency to focalization beneath the pleura and in the walls of relatively immobile structures like the sheaths of bloodvessels and bronchi. Although relatively small amounts are removed by way of the bronchi and by the lymphatic system to the tracheo-bronchial lymph nodes, it seems improbable, from the evidence at hand, that the lung would ever be able to rid itself of the major portion of the dust. Prolonged daily exposures finally cause an edematous condition in the bronchi and bronchioles which, however, rapidly subsides when the irritation is discontinued. The reaction of the normal lung to excessive quantities of this irritant is surprisingly insignificant. A true fibrosis in the parenchyma of the lung has never been observed. In the lymph nodes, on the other

hand, a definite fibrosis was frequently encountered. In the lung, in which carborundum inhalation is continued during the course of development of an inhalation tuberculosis, *extensive fibrosis is common*. The most remarkable result in this experiment has been the alteration in the course of the tuberculous process induced by the inhalation of this low virulent tubercle bacillus; from a self-limited process, which usually heals by resolution, it has been transformed into a progressive tuberculous bronchopneumonia. As a basis for this transformation it has been suggested that, through caseation of the primary focus, excessive amounts of dust have been liberated which attract new phagocytes to the area. By the agency of these phagocytes tubercle bacilli are accidentally transported to uninvolved portions of the lung and fresh foci of infection are established. Two other possible explanations have been suggested: (1) The mechanical obstruction to the drainage from the lung, as the result of fibrosis about the lymphatic vessels; (2) a direct effect of the dust upon the infecting organism. Opposed to the mechanical explanation is the observation that no fibrosis is present during the early stage of extension; later, when a generalized tuberculosis has developed, this factor may play some part. The argument that the bacillus may have been altered is met with the fact that there has been no serious extension to the abdominal viscera, such as regularly occurs when virulent bacilli are implanted in the lung tissue. In so far as proliferation of connective tissue may be considered as evidence of the ability of a mineral dust to injure pulmonary tissues, carborundum dust is apparently harmless to the normal lung, at least within the time limits of this experiment. If mere hardness and sharpness of a dust particle were sufficient to provoke fibroblastic proliferation characteristic of pneumokoniosis, carborundum dust should satisfy these conditions, for its hardness is between that of the ruby and the diamond, and its abrasive qualities are well known. The failure to produce this response in the lung may be considered negative evidence and favoring the chemical theory of the action of dust, which has been advanced by the English observers. As carborundum does not contain silicon in the crystalline form of silica, they would assume that it would not produce a silicosis. The mechanical hypothesis, suggested in explanation of the mechanism producing extension of partially healed tubercles, requires further investigation and will be controlled by the employment in a similar manner of other non-silicious dusts. However, it should always be borne in mind that silicosis in the human lung requires many years for its development and, while no hint of a proliferative process has been detected in the normal guinea-pig's lung, yet such a reaction might be produced if animals could be exposed for longer periods. The evidence for the solution of these problems is not to be found in such experiments as have been reported. These have been written more in the nature of preliminary communications than as finished results. They have served to determine the problems before us and to open up lines of investigation. Other work of a more fundamental character has been in progress for some time which, it is hoped, may illuminate the problem of the action of mineral dusts on pulmonary tissues.

Studies on the Paratyphoid-enteritidis Group: III. An Epidemic of Food Infection Due to a Paratyphoid Bacillus of Rodent Origin.—SALTHER and KRUMWIEDE (*Am. Jour. Hyg.*, 1924, 4, 23) report a food infection outbreak comprising fifty-nine cases. The cause of the outbreak was the contamination of the cream (cornstarch) filling of eclairs and crumb cake. The causative bacterium was a distinct paratyphoid type, *Bacillus pestis caviæ* (*Bacillus typhi murium*—"mutton type"), prevalent in rodents; it has also been isolated from one other species. This type, only recently separated with definiteness as a distinct and prevalent paratyphoid variety, is apparently one of the commonest etiological agents of food infection in man. The *Bacillus pestis caviæ*, *Bacillus cholera suis* and *Bacillus enteritidis* are apparently the three varieties most likely to be expected in cases of food infection. One gains the impression that, had the *Bacillus pestis caviæ* type been recognized earlier as a distinct paratyphoid type, it might have been found to be the most common of the three varieties.

Some Observations on Anopheles.—BARBER and HAYNE (*U. S. Pub. Health Repts.*, 1924, 39, 195), on the basis of observations made during the summer of 1920 and 1922 in a rice-growing region of Arkansas, state that anopheles in effective numbers spread about a mile from rice fields into an open country.

Some Observations on the Winter Activities of Anopheles in Southern United States.—BARBER, KOMP and HAYNE (*U. S. Pub. Health Repts.*, 1924, 39, 231) studied the subject with special reference to determining whether winter, when the number of mosquitoes was reduced, furnished a season which might be profitably employed in antimosquito work. The results from this point of view were not encouraging. All stages of anopheles, ova, larvæ, pupæ and adults were found throughout the winter in southern Georgia, Alabama and Louisiana. There is no true hibernation, active adults of all species studied being found.

Some Notes on the Relation of Domestic Animals to Anopheles.—BARBER and HAYNE (*U. S. Pub. Health Repts.*, 1924, 39, 139) sought to test the theory that domestic animals may serve, by furnishing a source of food for mosquitoes of the anopheles genus, to prevent the insects from biting man. They found that, given equal opportunities, mosquitoes fail to show preference for man, for the pig, or for the mule. It was also shown that feeding on pig's blood in no way impairs the taste of mosquitoes for human blood. The authors question, in general, the influence of animals in malaria prevalence.

Notice to Contributors.—All communications intended for insertion in the Original Department of this JOURNAL are received only *with the distinct understanding that they are contributed exclusively to this JOURNAL.*

Contributions from abroad written in a foreign language, if on examination they are found desirable for this JOURNAL, will be translated at its expense.

A limited number of reprints in pamphlet form, if desired, will be furnished to authors, *providing the request for them be written on the manuscript.*

All communications should be addressed to—

DR. JOHN H. MUSSER, JR., 262 S. 21st Street, Philadelphia, Pa., U. S. A.

THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

AUGUST, 1924

ORIGINAL ARTICLES.

THE USE OF TRYPARSAMIDE IN NEUROSYPHILIS.

BY W. F. LORENZ, M.D., A. S. LOEVENHART, M.D.,
THOS. F. REITZ, M.D.,

AND

C. P. ECK, M.D.

MADISON, WIS.

Introduction. Successful results with the use of tryparsamide in neurosyphilis have been reported by Lorenz, Loevenhart, Bleckwenn and Hodges,¹ who treated cases which were mostly of institutional types. The cases herewith presented are mainly ambulatory types of neurosyphilis such as are to be found in any large dispensary, and conform with the type of case that has been studied by Moore, Robinson and Keidel.² Our material has been classified in accordance with the clinical types defined by the Wisconsin group. In all of our cases, the diagnosis was based upon a thorough neurological examination together with complete serological findings.

Our serological examination comprised a Wassermann test of the blood serum performed in a manner that permitted of quantitative reading. The Wassermann reaction made with the spinal fluid was also performed by making a serial dilution of the fluid ranging from 0.2 to 1 cc. In addition, a cell count was made on the fresh fluid and any excess of globulin was estimated by the Ross-Jones and Noguchi butyric acid tests. A Lange colloidal-gold test was made with each fluid. With this complete information at hand our cases were separated into the following clinical groups: paresis, atypical paresis, asymptomatic paresis, meningovascular syphilis,

tabes and taboparesis. All the cases of neurosyphilis included in our report showed a pathological spinal fluid at some time in their course.

The clinical groups are defined in the following manner:

The requirements for the diagnosis of paresis were a definite mental abnormality associated with a positive Wassermann reaction of the blood and spinal fluid, a cell count ranging from 20 to 50 per c.mm., a positive globulin test and a paretic type of "gold sol." In addition to these serological findings there had to be present some neurological abnormality in the nature of pupillary changes, disturbance of reflexes, muscular incoördinations and other signs commonly seen in paresis.

The term "atypical paresis" is reserved for the cases presenting the clinical manifestations of paresis but with a negative blood Wassermann and atypical spinal fluid findings.

The term "asymptomatic paresis" we reserved for the cases which showed the serological and neurological characteristics of paresis but in which the mental picture was lacking.

The meningovascular types were predominantly cases that presented complaints of headache and dizziness with many neurological abnormalities usually better developed in paresis but nevertheless distinctly present in this group. The spinal fluid in meningovascular syphilis is usually differentiated from the paretic type by a lesser degree of positiveness in the Wassermann test—that is, larger amounts of fluid are required for a positive response. The cell count in meningovascular syphilis ranges from normal to very high counts of 200 and more. The "gold sol" usually shows a distinctive response with the maximum reaction in the third and fourth tubes. However, one not infrequently sees the typical paretic type of curve in this group. These latter are borderline clinical cases and difficult to differentiate from asymptomatic paresis.

No definition is required for tabes or taboparesis.

After the preliminary examination referred to, all of our cases were treated with tryparsamide and mercury salicylate. The tryparsamide was administered intravenously, usually in a dosage of 3 gm.; in a few instances, 2 gm. As a rule, one injection was given each week for a period of eight weeks. The drug was dissolved in 10 cc of freshly distilled sterile water and the solution filtered through a sterile filter paper before administering. The solution was injected at room temperature within a few minutes after filtering. Mercury salicylate was given intramuscularly in doses ranging from 32 to 65 mg. ($\frac{1}{2}$ to 1 gr.). These injections were spaced midway between the tryparsamide injections and a total of 8 doses of mercury salicylate given during the period of tryparsamide injection was the usual course of treatment.

The majority of our cases had received other forms of antiluetic treatment before tryparsamide and mercury was used. In general,

however, the results from previous treatment had been poor and our effort with this new drug was clearly warranted.

In all, we are reporting on 185 cases. The earlier cases have been in our hands since the spring of 1922. Many of our later cases, while included in this report, are still under treatment so that our results for the more recent cases cannot be regarded as final. However, considerable information has been obtained as the result of our efforts and the usefulness of this drug is further emphasized by our experience.

Paresis. We are reporting on 84 cases of paresis. While these were all ambulatory types, 9 were sufficiently psychotic, in our judgment, to warrant institutional supervision. Among the others some were distinctly euphoric and even delusional, with memory defects and other evidence of mental deterioration. In the majority of cases the mental symptoms were not so marked as to be recognized as a psychosis or detected as a grossly abnormal reaction. They might easily pass for normal. Yet, upon close inspection and inquiry ample evidence of reduced capacity for work, change in character, indifference, and lessened interests could be elicited. A small number were distinctly depressed. Others appeared dejected, and not infrequently expressed an awareness of mental confusion. Fatigability was frequently complained of by these less psychotic types. It is remarkable to note the frequency with which a distinct recognition of failing mental power is expressed by these early paretics. Probably one only sees these mental states in a dispensary practice.

It should be emphasized that in addition to the usual neurological signs of paresis, all of these cases showed a completely positive serology before treatment with tryparsamide and mercury.

The clinical results of treatment in this group are as follows: 37 cases (41 per cent) were mentally restored; 38 cases (42 per cent) were distinctly improved; 9 cases (10 per cent) remained unchanged; 6 cases (7 per cent) mental manifestations progressed.

By mental restoration we mean the disappearance of the mental symptoms noted before treatment which, in many cases, was further evidenced by a distinct increase in earning power. This change is invariably noticed by the patient himself as well as by those with whom he is closely associated, such as members of his family.

The effect of treatment on the serology was less marked. The blood Wassermann became negative in 49 cases (54 per cent); was reduced in 17 cases (19 per cent); remained stationary in 15 cases (17 per cent), and became more positive in 3 cases (3 per cent).

The spinal fluid findings were less influenced. In 6 cases (7 per cent) the fluid became completely normal. In 36 cases (40 per cent) a very marked improvement was noted. The cell content, which is most easily influenced by any form of treatment, fell to normal and greater amounts of fluid were required to bring about a positive Wassermann reaction.

The "gold sol" changed from the paretic type to that more frequently seen in meningovascular syphilis. In 24 cases (27 per cent) a final lumbar puncture could not be obtained. Of the remaining 17 cases (19 per cent) the spinal fluid serology remained practically unchanged, except for a reduction in cell count and some slight changes in the "gold sol" curve. These fluids were regarded as being uninfluenced. Most of these cases are still under treatment. In general a total of 24 gm. within a period of two months is required for any pronounced serological effect.

It is to be noted that the 6 cases with completely normal fluids after treatment with tryparsamide are among the cases that were restored clinically and that generally the cases which showed the maximum clinical improvement likewise showed the greatest serological improvement. There were two exceptions to this rule. One case showed an excellent clinical result after two courses consisting of 8 doses of 3 gm. each in which the blood and spinal fluid serology remained practically unchanged. The other case was one which showed complete clinical recovery after 3 courses of treatment, but in which the blood and spinal fluid were more positive serologically after the treatment. In both of these cases further therapeutic efforts will be made because it is feared that a strongly positive serology points to disease activity and therapy should be continued but possibly modified to meet the particular problem that presents itself.

Physical signs were but slightly influenced. However, the vast majority showed general improvement as evidenced by a gain in weight and improved general health and vigor. Some cases showed better muscular control and coördination, less disturbance of speech and less evident tremors. Pupillary anomalies remained practically unchanged.

The 36 cases that were mentally restored received from 16 to 48 doses of tryparsamide and mercury salicylate. All cases were started with 3 gm. In 2 cases the treatment was interrupted because of amblyopia but subsequently tryparsamide was resumed.

Paresis with Atypical Serology. Of the 90 paretics, we had 6 cases which from their mental and neurological findings would be clinically diagnosed as paretics, but in which the blood was negative and the spinal fluid atypical. These cases gave a history of intensive antiluetic treatment over a period of years. One of these cases presented the picture of paretic dementia that is usually found in the infirmary of a State Hospital. This particular case made a remarkable recovery after 16 injections of tryparsamide. The other 5 cases showed some improvement in their mental condition.

Asymptomatic Paresis. These cases showed the serological findings of paresis without mental derangement. Neurological symptoms were present in the nature of pupillary anomalies; disturbance of deep reflexes, tremors and frequently speech defects. These

cases can only be recognized as the result of routine spinal fluid examinations in all cases of positive blood in which syphilis has apparently been latent for long periods. The blood is very positive and the spinal fluid Wassermann is likewise positive with small amounts. The cell count is similar to that of paresis and the globulin tests are positive. In order to class the case as asymptomatic paresis, it was required that the "gold sol" be of the paretic type.

As these cases are predominantly serological conditions associated with physical signs which are slightly, if at all, affected by any anti-luetic treatment, the evidence of therapeutic effect therefore must be sought in the serology.

We include 23 cases of asymptomatic paresis in this report. As the result of treatment with tryparsamide and mercury, the blood Wassermann became negative in 19 cases. Of these, the spinal fluid of one became completely negative after 16 injections of 3 gm. each of tryparsamide. In 6 cases the spinal fluid was very markedly improved. The cell count was reduced to the normal range, the globulin tests became negative or only very faintly positive, and the Wassermann reaction either became completely negative or a positive reaction was obtained only with large amounts of fluid where small amounts had previously given a similar response. There was also a disappearance of the paretic type of "gold sol" reaction but a persistence of a reaction simulating that usually found in meningovascular syphilis. As a rule, the "gold sol" is favorably influenced early in the treatment but remains positive longer than the Wassermann test. In the 12 remaining cases in which the blood became negative, unfortunately lumbar punctures could not be obtained. It is possible that among these 12 patients, other cases of marked improvement in spinal fluid serology might have been found. It must be borne in mind that these patients suffer no symptoms. They are not very much worried about their condition and it is difficult to hold them for repeated lumbar punctures and other examinations.

Four cases showed practically no change in the blood or spinal fluid after 16 injections of tryparsamide and mercury. In 1 case the progress of the disease was apparently hastened. Definite mental symptoms developed during the second period of treatment. This patient was later committed to a State institution and no subsequent examination of the spinal fluid could be made.

Meningovascular Syphilis. In this group one has a clinical as well as a serological situation to observe during treatment. Here the patient suffers discomforts and evidences of improvement in his condition are both objective and subjective.

Twenty-nine cases were diagnosed as meningovascular syphilis. Of these 19 (66 per cent) recovered. The amount of treatment in these ranged from $2\frac{1}{2}$ to 5 courses or from 20 to 40 injections of tryparsamide over a period of from eight to twenty months. Seven cases were very much benefited but 3 remained unimproved.

In this group all the cases, with one exception, showed a positive spinal fluid before treatment was started. Before treatment 6 of the 29 cases had a negative blood with a positive spinal fluid. In 5 of the clinical recoveries both the blood and spinal fluid became completely negative. This represents 17 per cent in which a perfect result was obtained. In 13 cases of clinical recovery the fluid was markedly improved; in 7 cases it was favorably affected. The blood Wassermann became negative in 11 cases or approximately 48 per cent after 16 to 24 injections of tryparsamide. One of the cases included in the recoveries complained of severe headache, dizziness and mental fatigue and showed unequal pupils and exaggerated deep reflexes. His serology was negative before treatment. During the previous three years, this patient had received 20 injections of neoarsphenamin and over 40 injections of mercury. He was placed on tryparsamide in 3 gm. doses but no mercury was used. After 8 injections the symptoms had completely disappeared.

Tabes and Taboparesis. There are 43 cases of tabes and taboparesis included in this report. Of these, 14 showed definite mental symptoms which constitute the outstanding clinical manifestations. Mental restoration occurred in 3 of these cases, 7 improved and 4 remained practically unchanged. The 3 cases that showed the maximum mental restoration also showed the greatest serological improvement.

Of the 43 cases, 29 were tabetics. Most of these patients presented themselves for treatment because of severe crises. All had had previous antiluetic treatment without benefit. Ten cases were greatly relieved and claims of better health, better muscular control and general improvement were made by these patients. In 3 cases which were entirely relieved of pain, the improvement in muscular coördination was very evident. These patients had received from 32 to 40 injections of tryparsamide in 3 gm. doses.

The serological results in these cases were as follows: Sixteen of the 29 cases showed a positive blood before treatment: ten of these became negative after 2 to 3 courses.

Twenty-seven of the 29 cases showed a pathological spinal fluid but less marked than in paresis; that is, in some instances the "gold sol" alone was positive with a Wassermann reaction only positive with larger amounts of fluid and not infrequently with a normal cell count or only faintly positive globulin tests. In 3 cases the fluid became completely negative and in 16 cases decided improvement was noted.

In 16 of the 29 tabetics (55 per cent), treatment with tryparsamide and mercury was ineffective clinically. Two cases progressed rapidly and treatment was discontinued during the second course.

Visual Disturbance. Visual disturbance due to tryparsamide has been reported by Louise Pearce³ and by Lorenz, Loevenhart, Bleckwenn and Hodges.¹ All the cases treated by us were examined

before and during the period of treatment, The eye-grounds were frequently studied and the patient was tested for visual acuity. Inquiries as to visual embarrassment were frequently made during the course of treatment. There were no visual disturbances in the 23 cases of asymptomatic paresis. Among the 29 cases of meningo-vascular syphilis, 1 case developed very mild amblyopia. Treatment with tryparsamide was interrupted for two weeks and this symptom disappeared. The case was then carried on 2 gm. and later 3 gm. doses, as in the beginning, without developing any further visual disturbance. Of the 84 paretics, 2 cases developed amblyopia after 3 and 4 injections, respectively, of 3 gm. of tryparsamide. In both instances treatment was withheld for three weeks and then gradually resumed until the original 3 gm. dose was again being used. No further visual disturbance developed in these cases. Two cases of taboparesis developed amblyopia during the first course of treatment. Both of these were promptly relieved by withholding the drug for two weeks. As in the other cases mentioned treatment with tryparsamide was gradually resumed and continued without further trouble. Four cases of tabes developed a mild amblyopia and after a rest period treatment with tryparsamide was resumed without further visual disturbance.

In 4 cases a severe degree of visual disturbance occurred during the first course of treatment. Three of these were taboparetics and the other a case of tabes. In 1 case of taboparesis very definite optic atrophy was noted before treatment. In this case after 3 injections of 1 gm. the patient was able to distinguish only between light and darkness. The case has disappeared and we are unable to report the final condition. The other 3 cases of severe amblyopia were given no tryparsamide for one month. The visual acuity returned and these cases were then started on 1 gm. doses of tryparsamide. After 3 injections the dose was increased to 2 gm. and these patients were then continued on this dosage without any further recurrence of visual disturbance.

In all, 13 of the 185 cases of neurosyphilis or approximately 7 per cent showed visual disturbances. Nine of these cases were very mild and 4 were severe reactions. In 12 of 13 cases, all visual disturbances disappeared when the drug was stopped and all of these cases were subsequently treated with the original dose after they had been rested from two to four weeks.

It is noteworthy that the 4 severe cases developed in tabes and taboparesis and, further, that 6 of the milder reactions occurred in this group. A total of 10 of the 13 cases of visual disturbance occurred in tabetics and taboparetics and clearly points to the type of clinical case that must be watched with the greatest care.

The relationship of tryparsamide and other therapeutically used arsenicals to amblyopia is a problem that is being investigated by various members of our group. Extensive animal experimentation

by Young and Loevenhart⁴ has led to certain conclusions which will soon be reported. Another effort has been a special study in a large group of clinical cases by Bleckwenn and Neff. At this time we reiterate the need of careful eye examination before and during tryparsamide administration and the prompt withdrawal of this drug when amblyopia develops.

SUMMARY OF RESULTS OF THE THERAPEUTIC USE OF TRYPARSAMIDE IN NEUROSYPHILIS.

Classification.	Clinically.				Blood Wassermann.				Spinal fluid serology.			
	Restored.	Improved.	Unimproved.	Aggravated.	Negative.	Improved.	Unchanged.	More positive.	Negative.	Improved.	Unchanged.	Aggravated.
Paresis (90 cases)	37	38	9	6	49 ¹	17	15	3	6 ²	36	17	
Paresis, asymptomatic (23 cases)	There are no psychotic manifestations in this group. One case developed a psychosis during treatment.				19	..	4	..	1	6	4 ³	
Meningovascular syphilis (29 cases)	19	7	3	..	11 ⁴	6	6	..	5 ⁵	20		
Taboparesis (14 cases)	3	7	4	..	5 ⁶	2	2	..	1	10	3	
	(Psychotic cases only included.)											
Tabes (29 cases)	3	10	14	2	10 ⁷	..	6	..	3	16	10	

¹ Six cases had a negative blood before treatment with tryparsamide and are not included in the table.

² The table does not include the spinal-fluid findings in the 6 atypical cases and the 24 cases in which a final lumbar puncture was not obtained.

³ There were 12 cases in which final puncture was not obtained.

⁴ In 6 cases the blood was negative before treatment.

⁵ In 4 cases a final puncture was not obtained.

⁶ In 5 cases the blood was negative before treatment.

⁷ Thirteen cases were negative before treatment began.

Conclusions. As a result of our efforts in 185 cases of neurosyphilis treated over a two-year period, we conclude:

1. Tryparsamide and mercury salicylate are therapeutically effective in early paresis, meningovascular syphilis, and, to a lesser extent, in taboparesis, tabes and in advanced paresis.

2. The beneficial clinical results generally precede the improvement in the serology.

3. Definite parietic psychoses disappear as the result of treatment.

4. The mental restoration has persisted over a two-year period.

5. Visual disturbances occurred in 7 per cent of the total number treated.

6. In tabes and taboparesis 23 per cent of the cases showed visual disturbance.

7. Of 13 cases showing amblyopia during tryparsamide therapy all but one cleared up after the withdrawal of the drug. Twelve of these cases were subsequently treated with tryparsamide without further eye disturbance.

BIBLIOGRAPHY.

1. Lorenz, W. F., Loevenhart, A. S., Bleckwenn, W. J., Hodges, F. J.: Jour. Am. Med. Assn., 1923, 80, 1497.
2. Moore, J. E., Robinson, H. M., Keidel, A.: Jour. Am. Med. Assn., 1924, 82, 528.
3. Pearce, Louise: Jour. Exper. Med. (Supplement) 1921, 34, 1.
4. Young, A. G. and Loevenhart, A. S.: Jour. Pharm. and Exper. Therap., 1924, 23, 107.

CORONARY SCLEROSIS: AN ANALYSIS OF EIGHTY-SIX NECROPSIES.

BY FREDRICK A. WILLIUS, M.D.,

AND

GEORGE E. BROWN, M.D.,

SECTION ON MEDICINE, MAYO CLINIC, ROCHESTER, MINNESOTA.

IN the correlation of clinical data and necropsy findings one is sometimes impressed with the paucity of subjective and objective findings in the heart indicative of serious cardiac disease, when the pathologic findings demonstrate advanced sclerosis of the coronary arteries. This study was undertaken for the purpose of determining the frequency of occult coronary disease, and to obtain data to coördinate clinical and necropsy findings. Eighty-six unselected, consecutive, proved cases of coronary sclerosis were studied.

Age. The youngest patient in the group was thirty-three years of age, and the oldest eighty-one; the average age was sixty and three-tenths years. The highest incidence occurred in the seventh decade of life, in which there were 38 patients. There were 22 patients in the sixth decade, 17 in the eighth, 4 each in the fourth and fifth, and 1 in the ninth. It was interesting to find 4 cases of coronary sclerosis in the fourth decade and a well advanced process in a young person, aged thirty-three years; there was no evidence of syphilis in this patient. Hirschfelder mentions a colored boy, aged nineteen years, with sclerotic coronary arteries. The dominance of coronary sclerosis in the later decades of life, as revealed in this study, agrees with the general impression regarding age incidence.

Sex. There were 67 males (78 per cent), and 19 females (22 per cent) in the group. The marked dominance of the disease in males supports the findings of other observers.

Symptoms. Twenty-one patients (24 per cent) had had typical attacks of angina pectoris without evidence of heart failure. They uniformly had had very marked sclerosis of the coronary arteries, and 14 (66 per cent) had had pronounced occlusion of the lumen of the vessels. Three had had myocardial infarction. Four (19 per cent) had had associated syphilis of the aorta; 1 of these had had a saccular aneurysm, 7.5 cm. in diameter, above the left coronary orifice, and the other a diffuse aneurysmal dilatation of the arch. Syphilis has been considered a common etiologic factor in coronary sclerosis, yet in reality it plays a minor part.

Two patients (2 per cent) had had atypical anginal attacks; that is, the origin and distribution of pain were in unusual regions. Both patients had had pain in the epigastrium, with a tendency to radiate upward into the lower chest. The attacks bore a distinct relationship to exertion and to eating. One patient, a man, aged forty-five years, had had marked coronary sclerosis with the orifices nearly completely occluded by advanced syphilis of the aorta. The other patient, a man, aged seventy-two years, had had a moderate degree of coronary sclerosis with slight atheroma and distinct calcareous changes of the root of the aorta and the aortic valves. It is again difficult to diagnose these atypical anginal attacks.¹² The pain may occur in the abdomen, and may simulate almost any painful surgical disease of the abdomen.¹⁴

Twenty-two patients (26 per cent) had displayed the clinical syndrome of progressive myocardial failure unassociated with painful attacks. Two patients in this group had had severe paroxysms of dyspnea conforming to the so-called angina pectoris sine dolore type. One patient, besides progressive exertion dyspnea, had had severe attacks of paroxysmal ventricular tachycardia. The average sclerosis of the coronary arteries in this group was not so marked as in patients having typical anginal attacks. Only 5 patients (23 per cent) had had considerable occlusion of the arteries. Three patients had had infarctions of the myocardium. Only 1 patient had had syphilis of the aorta.

The progressive myocardial-failure type of coronary sclerosis apparently results from gradual interference in the circulation of the heart, producing progressive degenerative changes in the myocardium. It is probable that the heart may receive sufficient circulation to permit it to remain functional even in the presence of considerable sclerosis of the coronary arteries if there has not been a tendency toward occlusion. The degree and extent of myocardial degeneration depends, in part at least, on the degree of arterial obliteration, and on the length of time impairment in circulation has existed.

There were 7 patients (8 per cent) who, besides the progressive myocardial failure syndrome, had had typical attacks of angina pectoris. This group is emphasized because so many patients

suffering from angina pectoris present very little objective evidence of cardiac disease, and complain only of the anginal attacks. The average degree of coronary sclerosis in this group was marked. Four patients (57 per cent) had had considerable occlusion; 1 had had infarctions in the myocardium, and 1, besides sclerosis of the coronary arteries, had had well advanced syphilitic aortitis with involvement of the aortic valves.

Thirty-four patients (40 per cent) did not present sufficient subjective or objective evidence of cardiac disease to permit the diagnosis of coronary disease; their condition is referred to as the occult coronary type of disease. Osler emphasizes this observation in his statement that a large proportion of all patients with angina pectoris have clear-cut heart sounds and a good pulse and no obvious signs of cardiac disease, yet the coronary arteries may be extensively diseased. In this group the average degree of coronary sclerosis was considerably less than in the foregoing groups. Only 5 patients (15 per cent) had revealed evidence of coronary occlusion. There was none with myocardial infarction. One patient had had syphilitic arteriosclerosis of the aorta.

This important group of 34 patients deserves detailed consideration, as 40 per cent of the cases, or the largest subgroup of this study, disclosed no diagnostic evidence of coronary sclerosis. Sixteen of these patients were in the seventh decade of life, 9 in the eighth, 8 in the sixth, and 1 in the fourth. The outstanding complaints and findings had been: chronic nephritis in 6 cases, carcinoma of the stomach in 4 cases, carcinoma of the large bowel in 3 cases, peritonitis in 3 cases, diabetes mellitus in 3 cases, recent cerebral hemorrhage in 2 cases, benign prostatic hypertrophy in 2 cases, and pyonephrosis, inguinal hernia, non-syphilitic aneurysm of the abdominal aorta, chronic inanition, gastric ulcer, carcinoma of the prostate, spinal-cord tumor, splenomegaly of chronic splenitis, carcinoma of the pancreas, cirrhosis of the liver, and chronic pulmonary emphysema, in 1 case each. It is evident that a considerable degree of coronary sclerosis may exist with but few clinical signs, and it is important, therefore, always carefully to consider the possibility of occult coronary disease in patients in middle and later life.

Correlation of Associated Pathologic Findings. *Aorta.* In only one instance in this series was the thoracic aorta found to be normal. There had been syphilitic aortitis in 8 cases, in 2 of which aneurysmal dilatation had occurred, saccular in 1 case and diffuse in the other. The remaining 77 cases revealed varying degrees of sclerosis, atheroma, and ulceration of the aorta. The abdominal aorta revealed similar pathologic changes, well marked in 18 cases (21 per cent). In 1 case a large non-syphilitic aneurysm had ruptured into the right retroperitoneal space.

Heart Valves. The heart valves (leaflets or rings) were diseased in 44 cases (51 per cent). There was actual arteriosclerosis or fibrous thickening of the aortic valves alone in 17 cases (20 per cent), in 2 of which syphilitic aortitis was also associated. The mitral valves alone were sclerotic or fibrous in 6 cases (7 per cent). Both the aortic and mitral valves were the seat of sclerosis or fibrosis in 17 cases (20 per cent). In 2 cases (2 per cent) the aortic, mitral, and tricuspid valves were all involved. An acute vegetative tricuspid endocarditis was present in 1 case. In 1 there was marked sclerosis of all the valves.

The appreciation of the relative frequency of sclerosis and fibrosis of the cardiac valves associated with coronary sclerosis should aid the clinician in the interpretation of the auscultatory findings in older individuals. Only too often the murmurs noted with cardiovascular arteriosclerosis, and its attendant valvular insufficiencies are interpreted as indicating chronic valvular endocarditis.

Pulmonary Artery. The pulmonary artery was found to be diseased in only 4 cases (5 per cent). In 1 case the vessel was affected by marked arteriosclerosis; in another case it was dilated and contained chicken-fat clots, and in 2 it was the seat of quite extensive thrombosis.

Myocardium. In all the cases the myocardium had undergone various degenerative changes, consisting largely of fibrosis, fatty degeneration, cloudy swelling of the muscle bundles, segmentation, and fragmentation, and in 2 cases necrosis, in 1 of which brown atrophy had occurred. Seven cases (8 per cent) showed infarction of the myocardium. The weights of 63 hearts were recorded. The lowest weight was 140 gm. the highest, 1925 gm., and the average 472 gm.

Pericardium. The pericardium was diseased in 8 cases (9 per cent). Chronic adhesive pericarditis had occurred in 4, chronic fibrinous pericarditis in 2, and terminal fibrinous pericarditis and obliterating tuberculous pericarditis in 1.

Peripheral Arteriosclerosis. Sclerosis of the peripheral arteries was noted in 60 cases (70 per cent).

Renal Arteriosclerosis. Renal arteriosclerosis had occurred in 32 cases (37 per cent).

Cerebral Arteriosclerosis. The brains of 15 patients were examined and 13 of them revealed arteriosclerotic vessels.

Nephritis. Forty-six patients (53 per cent) had had varying degrees of chronic nephritis.

Disease of the Gall-bladder. Chronic cholecystitis, with or without stones, had occurred in 22 cases (26 per cent). This high incidence is probably partly coincidental, and partly due to the fact that the disease so often manifests itself in middle or later life, when arterial degenerative changes become evident. The association of disease of the gall-bladder with sclerosis of the coronary arteries sometimes

renders a correct diagnosis difficult, especially if the anginal attacks are atypical as regards distribution of pain.

Association of Hypertension and Coronary Sclerosis. The association of hypertension and coronary sclerosis is generally considered very unfavorable, especially in cases of angina pectoris. The added load cast on the heart by well advanced hypertension is considerable, and obviously enhances fatigue and degenerative changes of the myocardium. The myocardium, in most cases of coronary sclerosis, is already the seat of disturbances in nutrition, and any added insult undoubtedly increases the rate of progression and degree of structural damage. There were 29 cases of hypertension (33 per cent) in this series. The greatest incidence had occurred in both the fifth and sixth decades of life, 12 in each, 4 in the eighth, 5 in the seventh, and 1 in the fourth. The average blood-pressure readings in the hypertension group were systolic 183, diastolic 111, and pulse pressure 72.

It is difficult to estimate accurately the incidence of hypertension in this group, because the normal blood-pressure has not yet been definitely established for persons in the later decades of life. Wildt in his studies on blood-pressure and old age has shown that, between the ages of sixty and ninety, the systolic pressure range is from 137 to 162. At over ninety years, the systolic pressure decreases, and the diastolic is relatively low and does not follow the range of the systolic. In this series, the average blood-pressure in 16 cases in the seventh decade of life was systolic 146, and diastolic 86. There was moderate hypertension in 5 cases. In the sixth decade the average systolic pressure was 154 and the diastolic 91. Definite hypertension was present in 12 cases. In the fifth decade there were 21 cases in which the average systolic pressure was 133 and the diastolic 100. There was definite hypertension in 12 cases. There were too few cases in the fourth decade to obtain average values. The average systolic pressure readings decrease with advancing age. This may be explained by the fact that death occurs at an earlier age when hypertension and coronary sclerosis are associated, or that coronary sclerosis is comparatively rarer in primary vascular hypertension than in the senile or decrescent types of arteriosclerosis. In 9 cases (33 per cent) of typical angina pectoris, there was hypertension. In the progressive myocardial failure type, 12 cases (44 per cent) of hypertension were noted, and in the occult coronary sclerosis only 6 cases (22 per cent).

Association of Hypotension and Coronary Sclerosis. There were 3 instances of associated hypotension in the seventh decade of life, 9 in the sixth, and 2 in the fifth. The low blood-pressure in several cases was apparently related to the severe myocardial insufficiency which existed at the time of the patient's examination.

Association of Obesity and Coronary Sclerosis. The frequency of the association of obesity and degenerative cardiovascular disease

prompted the inquiry into this relationship, particularly with reference to sclerosis of the coronary arteries. The height and weight of 49 patients were available, 14 (29 per cent) of whom were distinctly obese. Twelve patients were males and 2 were females.

Mode of Death in Cases of Coronary Sclerosis. The frequency with which sudden death occurs in cases of coronary sclerosis has been noted for many years. In this series death occurred suddenly in 32 cases (37 per cent). The highest incidence, 12 (38 per cent), occurred in cases of typical angina pectoris. In the other clinical types of coronary sclerosis the order of frequency of sudden death was: in occult coronary disease, 7 cases (21 per cent), in angina pectoris with progressive myocardial failure, 6 cases (19 per cent), in progressive myocardial failure, 5 cases (16 per cent), and in atypical angina pectoris, 2 cases (6 per cent.)

Sudden death in cases of angina pectoris is not unexpected, but the rather high incidence in both the progressive myocardial failure, and the occult types of coronary sclerosis, implies the necessity for more accurate diagnosis and the identification of pathologic processes underlying myocardial degenerations. One case of sudden death was not attributable to coronary disease, but resulted from the rupture of an abdominal aneurysm.

A distinct degree of coronary occlusion had occurred in 18, 56 per cent of the patients who had died suddenly, or 62 per cent of the total number, 29, who had had coronary occlusion. Five patients had had infarction of the myocardium; 71 per cent of the sudden deaths occurred in this group.

Gradual Cardiac Failure. There were 13 cases (15 per cent) in which death had resulted from gradual myocardial failure. The incidence, according to clinical types, was angina pectoris in 5 cases (38 per cent), progressive myocardial failure in 5 cases (38 per cent), occult coronary disease in 2 cases (15 per cent), and angina pectoris with progressive myocardial failure in 1 case (8 per cent). The average degree of coronary sclerosis was marked, and 5 instances of occlusion were observed. In 1 case there was myocardial infarction, and in 1 syphilis of the aorta. Twenty-four per cent of the patients with angina pectoris died from gradual progressive myocardial failure.

Death Following Operation. Death occurred following operation in 21 cases (24 per cent), but in only 1 instance was death attributable to cardiac disease. The greatest number of patients operated on, 16 (76 per cent), had had the occult type of coronary disease. The operative procedures were numerous and the causes of death varied. Four of the patients (19 per cent) had had the progressive myocardial failure type of coronary sclerosis. One patient (5 per cent) with angina pectoris had been operated on. The average degree of coronary sclerosis in these cases was moderate; in 4 cases it was considerable. There was no instance of myocardial infarction.

Death from Other Causes. Twenty patients (23 per cent) died from causes other than those enumerated. Death in 12 cases of the occult coronary type of sclerosis resulted from chronic nephritis in 3 cases, cerebral hemorrhage in 2 cases, diabetic coma in 2 cases, carcinoma of the stomach, chronic inanition, carcinoma of the pancreas, cirrhosis of the liver, and chronic pulmonary emphysema in 1 case each. Six deaths from other causes occurred in the progressive myocardial failure type. Three deaths were attributable to cerebral hemorrhage, 1 to carcinoma of the prostate, 1 to diabetic coma, and 1 to suicide. In 1 case of those patients with angina pectoris and progressive myocardial failure type the cause of death was not clear. In 1 case of angina pectoris the patient committed suicide.

Electrocardiography in Coronary Sclerosis. The electrocardiogram is frequently of great value in aiding in the identification of coronary disease. The most common graphic abnormality is the negativity of the T-wave in certain isolated or combined derivatives. These, in order of importance, are: (1) in combined Derivations I and II, (2) in Derivation I alone, (3) in combined Derivations I, II, and III, and (4) in combined Derivations II and III. Definite electrocardiographic abnormalities, largely involving the T-wave, have been observed following sudden occlusion of the coronary arteries by embolism or thrombosis.^{5, 7} Smith, in his experimental coronary ligations in dogs, found quite constant alterations in the T-wave. In a previous study significant T-wave negativity was observed in 52 per cent of patients with angina pectoris.¹¹

Because of the importance of obtaining data regarding the correlation of electrocardiographic and necropsy findings, we are recording this relationship in detail. Twenty-five patients (29 per cent) had had electrocardiographic examinations.

Report of Cases. Case I (A341607).—A woman, aged thirty-five years, with angina pectoris of the progressive myocardial failure type, died suddenly. The electrocardiogram revealed auricular fibrillation, T-wave negativity in Derivation I, and preponderance of the left ventricle. At necropsy a moderate degree of coronary sclerosis, well advanced syphilitic aortitis, and incompetency of the aortic valves were noted. There was a moderate degree of dilatation of the left ventricle.

Case II (A264780).—A man, aged forty-two years, with angina pectoris died from gradual cardiac failure. The electrocardiogram revealed sinus rhythm and no abnormalities were noted. At necropsy the coronary arteries had numerous yellow tabular plaques of intimal thickening, and the vessels were patent and slightly dilated. Well advanced syphilitic aortitis, and diffuse aneurysmal dilatation of the arch existed. The cusps of the aortic and mitral valves were markedly sclerotic. There were many fatty deposits in the muscle bundles of the myocardium, and moderately increased connective tissue between the muscle bundles. The heart weighed 590 gm.

Case III (A399560).—A woman, aged fifty-five years, with the occult coronary type of disease, died from acute endocarditis following nephrectomy for pyonephrosis. The electrocardiogram revealed sinus rhythm, and no abnormalities. At necropsy the coronary arteries were moderately sclerosed, but not occluded. There were quite marked sclerosis of the aorta and acute vegetative endocarditis of the tricuspid valve. The myocardium was soft; there was slight separation of the muscle bundles with increased connective tissue. The heart weighed 375 gm.

Case IV (A394308).—A woman, aged fifty-two years, with the progressive myocardial failure type of disease, died from uremia, following thyroidectomy for adenomatous goiter with hyperthyroidism. The electrocardiogram revealed sinus rhythm, T-wave negativity in Derivation I, and preponderance of the left ventricle. At necropsy there were many raised yellow plaques of intimal thickening of the coronary arteries. There were similar changes of the intima of the aorta, extensive marked calcareous changes of the vessel, and vegetation of the right anterior cusp of the aortic valve. The myocardium was hypertrophied, of firm consistency, and brownish-red. An acute terminal fibrinous pericarditis was also noted. The heart weighed 500 gm.

Case V (A341702).—A man, aged fifty-seven years, with angina pectoris, committed suicide. The electrocardiogram revealed sinus bradycardia, T-wave negativity in Derivation I, and preponderance of the left ventricle. At necropsy the coronary arteries were found to be the seat of very marked and extensive sclerosis. There were syphilis of the aorta, areas of fibrosis of the muscle fibers of the ventricles, marked increase of subepicardial fat, and chronic fibrinous pericarditis.

Case VI (A344902).—A man, aged fifty-six years, with angina pectoris, died suddenly. The electrocardiogram revealed premature contractions of auricular origin and T-wave negativity in Derivation I. At necropsy the coronary arteries were very markedly sclerosed, with almost complete obliteration of the left orifice. The aorta was distinctly sclerotic, and there were numerous atheromatous ulcers and a moderate degree of myocardial degeneration. The heart weighed 400 gm.

Case VII (A386614).—A man, aged fifty-seven years, with the occult coronary type of disease, died following a herniotomy. The electrocardiogram revealed sinus rhythm and notching of the P-wave in all derivations. At necropsy marked sclerosis of the coronary arteries without occlusion was noted. The aorta likewise was very sclerotic, and there were many marked areas of ulcerating atheroma. The myocardium revealed a moderate degree of fragmentation and segmentation of the muscle bundles, and hypertrophy was marked. The left ventricle was dilated.

Case VIII (A394125).—A man, aged fifty-eight years, with angina

pectoris, died suddenly. The electrocardiogram revealed sinus rhythm, T-wave negativity in Derivation I, and preponderance of the left ventricle. At necropsy the coronary arteries were found to be markedly sclerotic, and the left coronary artery was almost completely obliterated. The aorta also was very sclerotic; elevated plaques occurred throughout its entire length, certain of which, near the bifurcation of the aorta, had undergone ulceration. There was arteriosclerotic thickening of the mitral and aortic valves. The muscle fibers of the myocardium were slightly enlarged, and the bundles revealed an abnormal separation. There was distinct atrophy of the wall of the left ventricle, with marked dilatation of the cavity. The heart weighed 525 gm.

Case IX (A42825).—A man, aged fifty-three years, with the progressive myocardial failure type of disease, died from gradual cardiac failure. The initial electrocardiographic tracing revealed auricular flutter with varying degrees of block, from 2:1 to 4:1. The ventricular rate varied from 83 to 169, and the auricular rate was 338 a minute. Five days later nodal tachycardia was present, and the following day sinus rhythm with marked prolongation of the P-R interval (0.32 second), evidently due to digitalis. At necropsy a moderate degree of sclerosis of the coronary arteries, and occlusion of the left descending branch by an old thrombus were noted. The aorta was moderately sclerotic, and numerous small ulcerations were found near the bifurcation. The myocardium was soft and flabby, and there were areas of focal hyalinization and fibrosis. There were a marked degree of fibrous tissue replacement in the interventricular septum, an aneurysm of the left ventricle at the site of infarction, and chronic adhesive pericarditis. The heart weighed 925 gm.

Case X (A148902).—A man, aged fifty-two years, with angina pectoris, died suddenly. The electrocardiogram revealed sinus rhythm and T-wave negativity in all derivations. At necropsy the coronary arteries were found to be markedly sclerotic and extensively occluded by thrombosis. The aorta was nodular, and the intima, fibrous, fatty, and calcareous. The myocardium revealed extensive fatty deposits, and a considerable degree of fibrosis. There was a marked degree of hypertrophy and moderate dilatation of the left ventricle. Infarction of the interventricular septum had occurred. The left ventricle was the seat of a mural thrombus. The aortic valves were fatty, fibrous and calcareous.

Case XI (A388891).—A man, aged sixty years, with the progressive myocardial failure type of disease, died from cardiac failure and bronchopneumonia. The electrocardiogram revealed premature contractions of ventricular origin, and T-wave negativity in combined Derivations I and II. At necropsy the coronary arteries and the aorta were found to be markedly sclerotic. There was extensive arteriosclerosis of the aortic endocardium. The myocardium

revealed a slight degree of fragmentation and segmentation of the muscle fibers. The left ventricle was hypertrophied. The heart weighed 700 gm.

Case XII (A399583).—A man, aged sixty-five years, with angina pectoris, died from gradual cardiac failure. The electrocardiogram revealed sinus rhythm and preponderance of the left ventricle. At necropsy sclerosis of the coronary arteries, producing almost complete obliteration, was noted. The aorta was also markedly sclerosed at its root, with atheromatous ulcers and thrombosis. A very marked sclerosis of the aortic valves occurred, producing incompetency. The myocardium showed fatty changes and a moderate degree of hypertrophy and dilatation. The endocardium of the left ventricle was diffusely thickened, showing small areas of erosion and ulceration, and a large ulcerated area to which a thrombus was attached. The heart weighed 500 gm.

Case XIII (A374229).—A man, aged sixty-three years, with the progressive myocardial failure type of disease, died in coma from diabetes mellitus. The electrocardiogram revealed sinus rhythm, diphasic T-wave in Derivation I and preponderance of the left ventricle. At necropsy there was marked sclerosis of the terminal coronary arteries. The aorta revealed an advanced degree of sclerosis with atheromatous ulcers. The pulmonary artery was markedly sclerosed. The heart weighed 400 gm.

Case XIV (A380262).—A man, aged sixty-eight years, with the progressive myocardial failure type of disease, died from arteriosclerotic gangrene of the left foot. The electrocardiogram revealed auricular fibrillation and preponderance of the left ventricle. At necropsy the coronary arteries were markedly thickened, the left being almost occluded. The intima of the aorta throughout its entire length, especially on its posterior surface, showed many areas of thickening with some calcareous changes. There was considerable hypertrophy of the myocardium with fibrosis. A ball thrombus was found in the left auricle and there was a mural thrombosis in the appendage of the right auricle. The heart weighed 400 gm.

Case XV (A323864).—A woman, aged sixty-nine years, with the progressive myocardial failure type of disease, died from bronchopneumonia and myocardial failure following thyroidectomy for adenomatous goiter with hyperthyroidism. The electrocardiogram revealed sinus tachycardia and preponderance of the left ventricle. At necropsy the coronary arteries were found to be markedly sclerotic, but there was no obliteration. The vessels were slightly dilated. The aorta and its large branches were very sclerotic, slightly dilated, and had areas of ulceration, particularly in the arch and below the celiac axis. The endocardium of the left ventricle was thickened and somewhat opaque, while the rings of the aortic and mitral valves showed numerous patches of yellow thickening. There was a slight degree of hypertrophy and dilatation of

the ventricles, and a moderate degree of fibrosis. The heart weighed 375 gm.

Case XVI (A327933).—A man, aged sixty-two years, with angina pectoris, died suddenly. The electrocardiogram revealed sinus rhythm and T-wave negativity in Derivation I. At necropsy a moderate degree of sclerosis of the coronary arteries was noted. On the root of the aorta and on the aortic and mitral valves were areas of yellow thickening. Only a slight increase in the connective tissue of the myocardium was noted. The heart weighed 550 gm.

Case XVII (A167754).—A man, aged sixty-one years, with the progressive myocardial failure type of disease, died from cerebral hemorrhage. The electrocardiogram revealed auricular fibrillation, T-wave negativity in Derivation I, and preponderance of the left ventricle. At necropsy many raised yellowish plaques of thickening in the intima of the coronary arteries and a few similar changes in the root of the aorta were noted. There was a slight diffuse fibrosis of the myocardium associated with a diffuse increase of fat. Hypertrophy was marked and dilatation was moderate.

Case XVIII (A192039).—A man, aged sixty-one years, with angina pectoris and the myocardial failure type of disease, died suddenly. The electrocardiogram revealed premature contractions of ventricular origin, T-wave negativity in all derivations, and preponderance of the left ventricle. At necropsy, numerous whitish areas of fatty and fibrous changes were noted in the intima of the coronary arteries, and similar areas in the aorta and the mitral valve. The heart was enormously enlarged and the myocardium revealed diffuse fatty degenerative changes.

Case XIX (A294006).—A man, aged sixty-four years, with the progressive myocardial failure type of disease, died from gradual cardiac failure. The electrocardiogram revealed sinus rhythm and T-wave negativity in combined Derivations II and III. At necropsy a moderate degree of sclerosis of the coronary arteries was noted. The aorta revealed moderate fatty and fibrous changes. Brown atrophy of the myocardium was quite marked, and there was a moderate degree of fibrosis. The mitral valves were definitely sclerotic.

Case XX (A70066).—A man, aged sixty-two years, with the progressive myocardial failure type of disease, with severe paroxysms of tachycardia, committed suicide. The electrocardiogram revealed ventricular tachycardia. At necropsy there was revealed a slight degree of sclerosis of the right coronary artery, with considerably more involvement of the left, particularly its descending branch. The aortic arch was slightly atheromatous. A few areas of fibrosis were scattered through the myocardium. The mitral and tricuspid valves were thickened and the aortic valves, besides being thickened, were slightly atheromatous.

Case XXI (A412224).—A man, aged seventy-four years, with

angina pectoris and the progressive myocardial failure type of disease, died from gradual cardiac failure. The electrocardiogram revealed sinus rhythm, T-wave negativity in Derivation I, and preponderance of the left ventricle. At necropsy the coronary arteries were extremely sclerotic, being almost completely obliterated by endarteritis. The aorta likewise was markedly sclerotic. The muscle fibers of the myocardium were hypertrophic and hazy. The ventricles were moderately hypertrophied but markedly dilated. There were mural thromboses in both ventricles. The heart weighed 725 gm.

Case XXII (A390697).—A man, aged seventy years, with the progressive myocardial failure type of disease, died from uremia associated with pyelonephritis and carcinoma of the prostate. The electrocardiogram revealed sinus tachycardia, negative P-wave in Derivation III, and preponderance of the left ventricle. At necropsy the left coronary artery was markedly sclerosed and almost totally obliterated, while the right coronary artery was enormously dilated. The aorta was markedly sclerotic, and there were marked fragmentation and segmentation of the muscle fibers of the myocardium. The aortic cusps were sclerotic along their line of attachment, and there was fenestration of all the cusps. The heart weighed 450 gm.

Case XXIII (A386550).—A man, aged seventy-one years, with the occult coronary type of disease, died from pyelonephritis and pneumonia following prostatectomy. The electrocardiogram revealed premature contractions of auricular origin, and preponderance of the right ventricle. At necropsy the coronary arteries were markedly sclerotic, but were not occluded. Over the posterior surface of the aorta were several raised yellow plaques varying in size; two in the descending aorta were ulcerated and showed calcareous changes. The margin of the left aortic cusp was fenestrated. Slight segmentation and fatty replacement of the myocardium were noted around some of the bloodvessels. The heart weighed 245 gm.

Case XXIV (A353997).—A man, aged seventy-eight years, with the progressive myocardial failure type of disease, died suddenly. The electrocardiogram revealed premature contractions of auricular origin, diphasic T-wave in Derivation I, and preponderance of the left ventricle. At necropsy marked arteriosclerosis of the coronary arteries with calcification was noted. The aorta was markedly sclerotic with raised plaques and areas of calcification; ulceration was most evident at the juncture of the larger vessels. The aortic endocardium was sclerotic and there was considerable aortic stenosis. There was marked sclerosis of the iliac arteries. The myocardium revealed degenerative changes and was hypertrophied.

Case XXV (A84930).—A man, aged seventy-one years, with the progressive myocardial failure type of disease, died from gradual cardiac failure. The electrocardiogram revealed premature con-

tractions of auricular and ventricular origin and preponderance of the left ventricle. At necropsy the intima of the coronary arteries revealed small, yellow, tabular plaques of thickening. The aorta was similarly involved, some of the areas showing ulceration and calcification. There was a moderate increase in the fibrous tissue of the myocardium between the muscle bundles, which varied in size and appeared granular on cut section. There was a moderate degree of hypertrophy and dilatation. The heart weighed 475 gm.

Discussion of Electrocardiograms. Seventeen of the cases (68 per cent), in which electrocardiographic examination was made, disclosed significant graphic abnormalities, as follows: (1) significant T-wave negativity in isolated and combined derivations in 12 cases, (2) auricular fibrillation with significant T-wave negativity in 2 cases, (3) uncomplicated auricular fibrillation in 1 case, (4) auricular flutter in 1, and (5) ventricular tachycardia in 1. It is significant that in 14 of the cases (82 per cent) in which there were important graphic abnormalities, there was significant T-wave negativity in the electrocardiograms. These, in order of frequency were: (1) T-wave negativity in Derivation I in 8 cases, (2) T-wave negativity in combined Derivations I, II, and III in 2 cases, (3) diphasic T-wave in Derivations I alone in 2 cases, (4) T-wave negativity in combined Derivations I and II in 1 case, and (5) T-wave negativity in combined Derivations II and III in 1 case. The high incidence of T-wave negativity in Derivation I alone is significant, and the occurrence of this abnormality should always direct attention to disease of the coronary arteries.

The question arises why there were no significant abnormalities in the electrocardiograms in 8 of the cases (32 per cent). Both gross and histologic study of the heart reveals only structural or anatomic changes, and affords little or no data with regard to disturbances in the physiologic processes. A critical study of Gross' work dealing with the coronary circulation, aids materially in correlating anatomic changes and the resultant disturbances in cardiac function. By the injection of opaque mediums into the coronary tree, Gross was able to produce remarkable roentgenograms of the arterial system of the heart. His specimens were all presumably normal, and averages in the various decades of life were studied comparatively and tabulated. Gross' work revealed two fundamental facts: (1) that with increasing age the anastomosis between the various branches of the coronary arteries was greater, and (2) that a definite metamorphosis occurred in the degree of vascular elements in the right and in the left side of the heart, definitely progressive according to decade. In the heart of the newborn a marked increase in the vascular elements of the right side of the heart over the left was evident; this diminished slightly, but remained dominant through the third decade of life. In the fourth decade the number and extent of the vascular elements of the left side become dominant and increase as the later

decades of life are approached; at this stage of Gross' specimens a remarkable diminution in the coronary branches of the right side of the heart occurs.

The progressive character in the diminution of the vascular elements of the right side of the heart in presumably normal specimens with the advent of age, and the marked degree which this reduced vascularity attains, are so striking that they may explain many obscure and apparent discrepancies between the gross structure of the human heart and clinical disturbances in its function. We must agree that our present methods do not permit a coördinated histologic study of the vascular structures of the heart. The nearest approach to a solution of this problem is the examination of the entire heart by serial section. This method is not only difficult, but extremely tedious, and precludes the study of large numbers of specimens. No coördinated study in a representative series of cases of the coronary tree in its entirety, in relationship to functional disturbances of the heart and studies in electrocardiography, has been made to our knowledge.

After a careful study of the reproductions of Gross' specimens, particularly of those of patients in the later decades of life, in which the blood supply of the right side is so definitely reduced, one can readily picture the condition that might exist with sclerosis of the coronary arteries. Assuming that the blood supply of the right side of the heart in older persons is already reduced, the further reduction from a superimposed sclerosis of these arteries could readily lead to a degree of avascularity, resulting in variable functional cardiac disturbances and in variable degrees of degenerative myocardial changes. The myocardial effects of coronary sclerosis are probably largely determined by the degree of anastomosis between the arterial branches, which varies even in the normal heart. With these observations in mind, the occurrence of normal electrocardiograms in certain patients with coronary sclerosis finds a tentative explanation at least.

Pardee and Master recently reported 11 cases of cardiac disease in which a correlation between clinical types, electrocardiographic findings, and necropsy data had been made. They found the coronary arteries diseased in all but 1 case. The anterior descending branch in 1 case was occluded by a thrombus, and considerable occlusion occurred in 2 other cases. In 6 cases (55 per cent) showing disease of the coronary arteries, the electrocardiograms revealed significant T-wave negativity, in order of frequency as follows: (1) in combined Derivations I and II in 3 cases, (2) in combined Derivations II and III in 2 cases, and (3) in Derivations I alone, in 1 case. In 2 cases there was T-wave negativity in all derivations, which was attributed to the administration of digitalis. These authors apparently regard these graphic abnormalities as of very little importance. The question is curtly dismissed by, "These various types of electro-

cardiographic abnormality have been considered to be associated with abnormality of the ventricular muscle, but the evidence for this is only of circumstantial character."

We have repeatedly studied large groups of cases in which there was significant T-wave negativity in the electrocardiograms, and have repeatedly called attention to the high cardiac mortality attending these disorders.^{10, 13} Our results have recently been confirmed by MacIlwaine and Campbell, who found even higher mortality averages. We believe that the accumulated data regarding the importance of significant T-wave negativity as indicative of serious myocardial disturbances has attained a position where evidence supporting its value can hardly be referred to as circumstantial.

Summary. The average age of the patients was sixty and three-tenths years; the youngest was thirty-three, and the oldest eighty-one. There were 67 males (78 per cent) and 19 females (22 per cent). The symptoms were arbitrarily classified as: (1) typical angina pectoris, 21 cases (24 per cent), (2) atypical angina pectoris, 2 cases (2 per cent), (3) the syndrome of progressive myocardial failure unassociated with painful attacks, 22 cases (26 per cent), (4) the syndrome of progressive myocardial failure and typical angina pectoris, 7 cases (8 per cent), and (5) the occult type of coronary sclerosis in which insufficient subjective or objective evidence of cardiac disease existed to permit its clinical identification, 34 cases (40 per cent).

The degree and extent of sclerosis of the coronary arteries in relation to the clinical types is discussed with special reference to vessel occlusion resulting from sclerosis, thrombosis and embolism.

The aorta was found diseased in all but 1 case; it was syphilitic in 8 cases (9 per cent). There was aneurysm in 3 cases: in 2 cases involving the thoracic aorta, and in 1, the abdominal aorta.

The heart valves were diseased in 44 cases (51 per cent), and the pulmonary artery in 4 (5 per cent). In all cases there were degenerative myocardial changes. Associated disease of the pericardium occurred in 8 cases (9 per cent). Peripheral arteriosclerosis was noted in 60 cases (70 per cent), renal arteriosclerosis in 32 cases (37 per cent), and cerebral arteriosclerosis in 13 of the 15 brains examined. Forty-six patients (53 per cent) had had varying degrees of nephritis. The gall-bladder had been diseased in 22 cases (26 per cent).

Twenty-seven patients (31 per cent) had had hypertension; the average readings were systolic 183, diastolic 111, and pulse pressure 72. Fourteen patients (16 per cent) had had hypotension. Fourteen (29 per cent) of 49 patients, whose height and weight were recorded, were obese.

Sudden death occurred in 32 cases (37 per cent), in order of frequency in the clinical groups as follows: typical angina pectoris in

12 cases (38 per cent), occult coronary type in 7 cases (21 per cent), angina pectoris with progressive myocardial failure type in 6 cases (19 per cent), progressive myocardial failure type in 5 cases (16 per cent), and atypical angina pectoris in 2 cases (6 per cent).

Gradual cardiac failure occurred in 13 cases (15 per cent). The incidence according to clinical types was: (1) angina pectoris in 5 cases (38 per cent), (2) progressive myocardial failure type in 5 cases (38 per cent), (3) occult coronary disease in 2 cases (15 per cent), and (4) angina pectoris with progressive myocardial failure type in 1 case (8 per cent).

Death following surgical operation resulted from various causes in 21 cases (24 per cent), but in only 1 was it attributable to cardiac disease.

Death was due to other causes in 22 cases (23 per cent).°

Twenty-five patients (29 per cent) had had electrocardiographic examination, 17 of whom (68 per cent) had revealed significant graphic abnormalities. These findings were: (1) significant T-wave negativity in isolated and combined derivations in 12 cases, (2) auricular fibrillation with significant T-wave negativity in 2 cases, (3) uncomplicated auricular fibrillation in 1 case, (4) auricular flutter in 1 case, and (5) ventricular tachycardia in 1 case.

BIBLIOGRAPHY.

1. Gross, L.: *The Blood Supply of the Heart*, New York, Hoeber, 1921.
2. Hirschfelder, A. D.: *Diseases of the Heart and Aorta*, Philadelphia, Lippincott, 1918, p. 381.
3. MacIlwaine, J. E., and Campbell, S. B. B.: *Ventricular Complex of the Electrocardiogram as a Physical Sign in Cardiac Prognosis*, *Brit. Med. Jour.*, 1923, 2, 456.
4. Osler, W.: *The Principles and Practice of Medicine*, New York, Appleton, 1919, p. 840.
5. Pardee, H. E. B.: *An Electrocardiographic Sign of Coronary Artery Obstruction*, *Arch. Int. Med.*, 1920, 26, 244.
6. Pardee, H. E. B., and Master, A. M.: *Electrocardiograms and Heart Muscle Disease. Preliminary Report*, *Jour. Am. Med. Assn.*, 1923, 80, 98.
7. Smith, F. M.: *The Ligation of Coronary Arteries with Electrocardiographic Study*, *Arch. Int. Med.*, 1918, 22, 8.
8. Smith, F. M.: *Electrocardiographic Changes following Occlusion of the Left Coronary Artery*, *Arch. Int. Med.*, 1923, 32, 496.
9. Wildt, H.: *Ueber Blutdruck im Greisenalter*, *Zentralbl. f. Herz. u. Gefass.*, 1912, 4, 41.
10. Willius, F. A.: *Observations on Negativity of the Final Ventricular T-Wave of the Electrocardiogram*, *Am. Jour. Med. Sci.*, 1920, 160, 844.
11. Willius, F. A.: *Angina Pectoris; an Electrocardiographic Study*, *Arch. Int. Med.*, 1921, 27, 184.
12. Willius, F. A.: *Atypical Pain with Angina Pectoris*, *Med. Clin. N. Amer.*, 1921, 5, 371.
13. Willius, F. A.: *Electrocardiography and Prognosis. I. Significant T-wave Negativity in Isolated and Combined Derivations of the Electrocardiogram*, *Arch. Int. Med.*, 1922, 30, 434.
14. Willius, F. A.: *Angina Pectoris and Surgical Disease of the Abdomen*. In press.

**CORONARY ARTERIAL OCCLUSION: A PERFECTLY DEFINITE
SYMPTOM-COMPLEX; THE REPORT OF THIRTEEN
CASES WITH ONE AUTOPSY.**

BY HERMON C. GORDINIER, M.D.,

TROY, N. Y.

CORONARY arterial occlusion with cardiac infarction has until recently been recognized only as a pathological curiosity at the autopsy table. It is only during the past decade or two, through the results of careful physiological experimentation and clinico-pathological observations, that a definite complex of symptoms have been portrayed characteristic of occlusion of these arteries. The cases herein recorded, 13 in number, have been carefully studied, and each one found to present the subjective symptoms and physical signs considered diagnostic of this clinical entity. Of the 5 fatal cases but 1 came to autopsy. This case showed a definite thrombosis of a large descending branch of the left coronary artery with a fresh cardiac infarct.

The coronary arteries, although considered physiological end-arteries, communicate, especially their smaller branches, in a most remarkable mesh of fine arterioles and capillaries. This very free anastomosis has been beautifully demonstrated by Gross, Baldwin, Jamin, Merkel, Ordway, Hirsch and Spalteholtz and others from the study of stereoscopical roentgen-ray photographs taken from carefully prepared and injected coronary vessels of man and animals.

The experimental occlusion of the coronary arteries in animals by Porter, in 1893, showed that when the main coronary arteries were plugged sudden death in all animals occurred; whereas, when the circumflex vessels were occluded death occurred in 10 per cent, and in only 50 per cent of the animals when the large descending branches were involved. Death as a result of the occlusion of these large branches was instantaneous or in a few hours or days, death often being preceded by auricular or ventricular fibrillation.

Porter's experiments seemed to show that the results of such operations varied according to the amount of myocardium deprived of its blood supply. When the smaller arteries alone were occluded, such as the arteria septi and the small descending branches, the heart was not seriously affected.

The pathological changes most frequently found associated with occlusion of the coronary arteries, apart from the infarcted area of the myocardium and the subsequent changes resulting therefrom, are atheromatous changes of the presigmoid part of the aortic arch, including the sinuses of Valsalva and mouths of the coronaries. Similar changes in the coronary arteries, aneurysm of the thoracic aorta, infectious and syphilitic mesaortitis, syphilitic

endarteritis, obliterating arteritis, general arteriosclerosis, chronic pericardial adhesions and myocardial degeneration. Sudden embolic plugging may occur in septicemia and pyemia or during the course of septic or simple endocarditis or from the disentanglement of mural thrombi from the cardiac chambers, and especially may they be detached from the muscoli pectinati of the auricular appendages.

As a result of the plugging of a branch of a coronary artery by a thrombus or embolus, there occurs an anemic infarct with an area, small or large, of myomalacia. If this area is small it goes on to repair by connective-tissue substitution or fibrosis, leaving a small area of scar tissue which does not, save transiently, impair the myocardial function. If, on the other hand, a large area of softening occurs from the plugging of a large branch, permanent and very serious myocardial insufficiency may result, or aneurysmal dilatation of the ventricular wall may occur, or a true ventricular aneurysm appear with early rupture, or ventricular puncture may occur with, in both instances, sudden death from hemopericardium.

The symptoms of thrombosis of the coronary arteries are quite characteristic and form a definite group or complex easy of recognition and pathognomonic of this condition.

For the recognition clinically of thrombosis of the coronary arteries and the presentation of this characteristic syndrome we are especially indebted to the studies of Sir William Osler, George Dock, Sir Clifford Allbutt, Krehl, Sternberg, Whittington Gorham, Libman, and Herrick and his co-workers. This complex consists of the following important symptoms, many of which are abrupt in their onset.

Pain.—Sudden excruciating anginoid pain, substernal (angina pectoris) or upper abdominal (angina abdominalis) in character, with or without the characteristic radiation of true angina pectoris.

The pain is usually of great severity and if the patient, as so frequently happens, has been subject to previous attacks of angina pectoris, he will state that the pain of this attack is much more atrocious than that of any previous one. The pain in most cases continues unabated for several hours or days "status anginosus," or rarely it may be but transient or it may recur at short intervals.

As stated above, the pain not so infrequently takes its origin or is referred to the upper abdomen, and because it is often associated with vomiting, gaseous distention and upper recti muscle spasm it has often been mistaken for an acute inflammatory condition of the abdomen, such as an appendix or gall-bladder, perforation of a gastric or duodenal ulcer, hemorrhagic pancreatitis or a sudden intestinal block, and in consequence therefore of such error some of these sufferers have been subjected to unwise and needless surgical intervention.

Facies. The facial expression is one of great anxiety, the color is pale, leaden or ashen gray; the skin is cold and bedewed with sweat; the features are pinched and the expression indicative of great pain, shock and extreme exhaustion; recurring fainting attacks may occur on the slightest exertion, while that curious mental phenomenon *angor animi*, or feeling of immediate dissolution, is rather common.

In most all cases (all but 3 of this series) an acute emphysematous distention of the thorax suddenly appears, and this condition is usually associated with great dyspnea, which may amount to extreme orthopnea, with variable degrees of cyanosis and moist crackling rales from passive hyperemia, and edema of the bases of the lungs. Extensive pulmonary edema was present at the onset in 10 of the cases herein recorded, and extreme air-hunger was a noteworthy symptom in all but 2 of the cases.

Pulse. The pulse is often rapid, easily compressed and thready; in many cases it soon becomes grossly irregular. The vessel wall is usually found thickened, although in 3 of my cases both the radial and temporal arteries were palpably normal. The systolic blood-pressure in most cases suddenly falls, while the diastolic is usually sustained and the pulse pressure correspondingly narrowed. This sudden drop in the systolic blood-pressure has been observed in such a large number of cases that, taken with the other symptoms, it may be justly regarded as of considerable diagnostic value.

Heart. The cardiac impulse is often a diffuse feeble tap, or it is not visible or palpable. The heart sounds are distant, the action usually tumultuously irregular and a gallop or tic-tac rhythm is rather frequently observed. Auricular fibrillation is, perhaps, the most commonly observed type of arrhythmia, and is of diagnostic significance if occurring for the first time with the above described symptoms. Pulsus alternans, acute auricular flutter, repeated extrasystoles, auriculoventricular and arborization block are not infrequently found; paroxysmal tachycardia of ventricular origin has also been observed in a few cases, most of which have been fatal. Acute dilatation of the heart is common and may be recognized by a sudden increase in its transverse diameter, both to the right and left, and distant feeble heart sounds, a gallop or tic-tac rhythm, associated with the sudden onset of the symptoms of myocardial insufficiency.

Pericardial Friction. By far the most characteristic diagnostic sign, if not absolutely pathognomonic of this symptom-complex is, as so well described by Gorham, the presence of a strictly localized, evanescent, to-and-fro pericardial friction rub, due to a roughening of the pericardial surfaces from a fibrinous exudate overlying the area of the myocardial infarct and appearing within a few hours, or a day or two or three after the abrupt onset of myocardial insufficiency. The pericardial rub is often difficult to

detect and must be most conscientiously sought for at each visit, otherwise it may be entirely overlooked. Gorham found it present in 5 of his 6 cases reported in the *Albany Medical Annals* for April, 1920. He believes that in the 1 case its absence may be explained by the fact that the infarcted area was on the posterior aspect of the left ventricle and a hemopericardium had developed. It was present in 11 of the 13 cases herein reported and may have been present early in 1 case, as the patient was seen some two weeks after the original insult, and he assured me that his heart had not been examined.

In most cases a fever of a mild type develops and lasts for a few days to a week. It is usually associated with a slight or moderate polymorphonuclear leukocytosis. Both of these symptoms may result from protein absorption from the softened infarcted area. While the failure to detect or the absence of a pericardial friction rub does not invalidate the diagnosis of coronary artery occlusion, its presence, particularly if associated with the above described symptoms of acute myocardial insufficiency, is of great diagnostic significance and serves to make the diagnosis positive.

Electrocardiographical Changes. R. Herrick has recently shown from a clinical study of several cases of thrombosis of the coronary arteries that the T-wave is inverted in leads I and II of the electrocardiogram and that evidence of arborization block is not infrequently found.

His colleague, Smith, has confirmed these results experimentally in animals by ligation of the descending branches of the left coronary artery. The experiment showed an immediate exaggeration of T-wave and its return within twenty-four hours to negativity, to be followed later to its positive position and then to return to a final iso-electric or negative position. These changes were not noted when the right circumflex branches were so operated. Herrick and Smith believe that the above described electrocardiographical changes are diagnostic of coronary artery occlusion in man and animals.

Morris Kahn states that this change of the T-wave from a strongly positive peak to a markedly negative one, and then a slow return to the positive or iso-electric form, is so characteristic experimentally that similar changes in this wave in man may reasonably be supposed to be due to similar lesions in the left coronary artery. Ventricular paroxysmal tachycardia has been observed by Robinson and Hermann in 4 cases clinically of occlusion of the coronary arteries, in 1 of which a fresh thrombus was found at autopsy.

Four types of cases of coronary artery occlusion are observed:

1. Cases, not at all rare, where death is very sudden, preceded or not by terrific substernal pain. Autopsy only discloses the true nature of the condition.

2. Cases which are preceded by the above described subjective

symptoms and physical signs of coronary artery occlusion, death occurring suddenly or in a few hours or days.

3. Cases in which death is due to myocardial insufficiency weeks or months after the characteristic abrupt stormy onset.

4. Cases, 8 in this series, with abrupt onset with all the clinical manifestations of this entity, which eventually make a fairly good recovery but with a diminished cardiac reserve.

Case Reports. CASE I.—Angina pectoris; sudden death; thrombosis of a descending branch of the left coronary artery with a fresh cardiac infarct; no pericardial friction rub audible. (Autopsy.)

H. F. L., aged seventy-three years, a farmer, entered the Mary McClellan Hospital, March 21, 1920, complaining of shortness of breath and substernal pain.

History. The family history was without import save that his father and mother lived to be very old and died of senility. He had had the usual childhood diseases since which time until the onset of the present illness he always enjoyed good health.

The present illness began about two weeks ago, when following the drinking of a large quantity of cider he became very nauseated; he vomited several times and a severe diarrhea ensued. The evening of the day in which this digestive upset occurred he became extremely short of breath and had to sit up in bed all night. At first he had a dry unproductive cough, which later became quite loose. At the same time he experienced a dull but rather severe pain in the region of the middle of the chest which did not radiate. He had no edema of the limbs, trunk or face.

Physical Examination. He was fairly well nourished; his facial expression was anxious and he was quite pale. There was no edema and his respirations were hurried. He was propped up in bed and suffered with dyspnea. His cranial nerves were intact, with the exception that the pupils did not react to light either direct or consensually, and an external strabismus of the left eye existed. The eye-grounds showed definite evidences of arteriosclerosis. The chest was emphysematous in type. The lungs were hyperresonant throughout. This vesiculotympanic note obscured both the cardiac and upper liver dullness. The expiration was prolonged and low in pitch in the clavicular regions. There were a few moist crackling rales at the bases.

Heart: The cardiac impulse was not visible or palpable; a distinct diffuse epigastric pulsation was present. The heart sounds were feeble and distant. The aortic second sound was louder than the pulmonic. There was no endocardial or exocardial murmurs. The pulse-rate was 86; it is regular but feeble; the vessel wall was very much thickened. The cardiac area could not be made out because of the hyperresonant note.

The liver could not be palpated. There was no tenderness in the region of the gall-bladder; it could not be palpated.

The abdomen was not distended; no muscle spasm existed; no evidence of free fluid, splash, tumor mass or herniæ.

The spleen could not be outlined either by percussion or palpation. The extremities were free; motion and sensation were intact; the reflexes were normal.

Course. There was a slight rise of temperature during his stay in the hospital. Urinalysis showed nothing abnormal. The patient seemed gradually to improve each day until March 29, when, while talking to a patient in an adjoining bed, he suddenly became very cyanosed and expired.

Autopsy showed very marked sclerosis of both coronary arteries, with a fresh thrombus in one of the descending branches of the left coronary artery and in the left ventricular wall, near the apex, an area of softening about 4 cm. wide. This recent infarct was thinned, velvety and red in color. The lungs were very emphysematous but otherwise normal. The pulmonary artery was not thrombosed. The gall-bladder contained a number of gall stones.

In this case the pericardial friction was missed, doubtless because the original attack of angina occurred two weeks before he entered the hospital, and the chest had not then been examined.

CASE II.—Chronic myocarditis; angina pectoris; coronary artery occlusion; acute cardiac decompensation. (Recovery.)

Mrs. I. H. H., aged fifty-two years, was admitted to the Mary McClellan Hospital, June 28, 1920, complaining of precordial pain, cough, dyspnea and great weakness.

History. Her family history was without import. She had been a sufferer for four years with diabetes mellitus, otherwise she had had no illness since childhood. She has one living child; no still-born or miscarriages.

The present illness had begun three days before, with a severe pain in the region of the sternum which came on suddenly; it lasted but a few minutes, only to be repeated six hours later with great severity and with the sense of intense substernal pressure. This pain and pressure discomfort disappeared the following morning.

Examination. A woman of medium build; was slightly cyanotic, very dyspneic, with anxious facial expression, ashen color, but with no edema. The lungs were hyperresonant; fine moist rales were present at the bases.

Heart: Distinct tenderness on pressure existed over the precordial region. The cardiac dulness at the level of the fourth rib was increased to the left to the mid-clavicular line and to the right 1 cm of the sternal margin. The heart sounds could be only feebly heard. There was a definite gallop rhythm; no friction or endocardial murmurs were present.

Course. June 29 a definite rough pericardial friction rub at the junction of the third left costal cartilage with the sternum was heard, localized to an area the size of a silver quarter of a dollar, and increased in intensity by the pressure of the chest-piece of the stethoscope, which also brought out tenderness and excited pain. The pulse was irregular, rapid and compressible. The blood-pressure was 110/80 mm.

On July 3 the patient seemed better; there was no dyspnea, cyanosis or edema. The pericardial friction was distinct; the pulse was regular; the blood-pressure 115/80 mm. She complained of mild substernal pain, extending out to the left axilla.

July 26 the patient was in bed. Respirations were normal; color, pink; rhythm, regular; heart sounds, clear but distant; no friction; no constriction or precordial pain or uneasiness.

She was discharged, August 10, 1920. During her stay in the hospital sugar and casts were constantly found in the urine. Her temperature ranged from 99° to 101° F. for a period of three weeks.

December 24, 1922, she was still alive and was able to do light housework and exercise moderately without much discomfort.

CASE III.—Occlusion of a coronary artery with sudden death.
(No autopsy.)

Mr. F. E., aged sixty-eight years, was seen in consultation with Dr. Otis Z. Bouton, of Fultonville, N. Y., on September 18, 1918.

History. Four brothers died of angina pectoris. One died after the onset of a very severe attack of substernal pain; one died two weeks after recurring attacks of angina pectoris, "coronary thrombosis." The other two brothers had been sufferers from angina and both died suddenly.

The patient had always been well until January 26, 1916, when, following a severe cold, he developed acute hemorrhagic nephritis, from which he apparently made an excellent recovery.

April 15 he was treated for a severe attack of influenza, which confined him to bed about ten days.

August 23 Dr. Bouton received an urgent call, and found the patient with an anxious expression, pale, bedewed with sweat and complaining of a squeezing, crushing pain beneath the sternum, running down the left arm to the little and ring fingers. He stated that for the past few weeks the slightest exertion had brought on similar, though much milder attacks. He was relieved by glonoin and morphin. His blood-pressure was not taken. His pulse was regular and not accelerated.

August 28 he went to the doctor's office and expressed himself as feeling better, but was very weak. His blood-pressure was 100/80 mm.; the heart sounds were weak; a soft systolic apical murmur was heard.

On September 3 he had another attack of substernal pain, not as

severe as the first attack, but followed by great prostration, considerable dyspnea, anxious, pinched facies and cyanosis.

I saw him two days later and found him semi-erect in bed, with respirations quickened and shallow, lips and fingers blue, with slight soft edema about the tibiæ and ankles. The pulse was 110, very irregular and thready; vessel walls were thickened; the heart's impulse was feeble and diffuse, its action tumultuous and a soft systolic mitral murmur and a very typical to-and-fro superficial pericardial friction sound were heard just within the site of the impulse, covering an area about 2 cm. in diameter. The heart sounds were distant. The cardiac dulness extended 10.5 cm. to the left of the mid-sternal line and 3 cm. to the right. The blood-pressure was 90/70 mm.

The lungs were hyperresonant throughout, and numerous bubbling subcrepitant rales were present at the bases. His temperature was 97.8; no cell count was made. The urine contained a trace of albumin.

The patient continued as above described until September 12, 1918, when he had another attack of substernal pain, and died before the doctor could reach him. A postmortem examination was not allowed.

This case is of particular interest because of the fact that four brothers died of what had been diagnosed as attacks of angina pectoris—three suddenly, shortly after the onset of angina pectoris, and one two weeks after recurring attacks of angina, probably of coronary arterial thrombosis.

CASE IV.—Thrombosis of a coronary artery with the rapid onset of acute heart failure and death. (No autopsy.)

The patient was a male, aged forty-eight years, of French descent, a mill-worker; he was married, with wife living, and the father of four healthy children. He denied venereal disease. His habits were excellent; he used neither tobacco or alcohol.

History. In the autumn of 1922, while undergoing an examination for a life insurance, it was found that his systolic blood-pressure was 240 mm. He had, however, no cardiac embarrassment; in fact, he appeared and felt in excellent health.

March 9, 1923, while returning home from work, he stopped at the office of his physician, because of severe pain in the mid-epigastric region, which became most agonizing, and he felt as if he would die; the pain radiated to the left shoulder.

The doctor stated that his features were pinched, that he was blanched and appeared like one suffering from great shock. For a few seconds he could not palpate the pulse at the wrist. He gave him stimulants and a hypodermic of morphin and atropin and several doses of nitroglycerin.

In the course of an hour his pain was some improved and the

doctor took him to his home. His pulse was thready, rapid and irregular; the heart's action was tumultuous. The following day he still had some uneasiness in the substernal region and his chest felt sore. The breathing was rapid and short, and many moist rales existed at the lung bases.

The second day after the onset of the severe anguish the doctor discovered a rough to-and-fro superficial friction rub over the body of the sternum at about the junction of the fourth costal cartilage. This continued for two days and then became inaudible. It was noticed at this visit that the urine which he passed was bloody, but there was no pain or frequency. Shortly after the onset it was also noticed that in addition to his extreme exhaustion, breathlessness and palpitation, that his feet and ankles were swollen and this edema gradually extended upward. The hematuria soon ceased, but the quantity was greatly reduced.

On June 5 I saw the patient with Dr. S., his physician, and found him sitting upright in an arm chair, unable to lie down because of the extreme dyspnea. Soft edema of the extremities and trunk were present, his complexion was sallow and his lips, finger tips and ears violaceous. The pulse-rate was 80, and it was easily compressed and very irregular—a medley of feeble and rather strong beats; the vessel walls were thickened. The cardiac impulse was feeble and diffuse, and no thrill of friction was palpable. There was heard a soft systolic apical murmur not conducted (relative mitral insufficiency?). No pericardial friction rub. The cardiac dulness was 14 cm. to the left and 4 cm. to the right of the mid-sternal line. A pulse deficit of 50 was present, the rate at the impulse being 130. A definite gallop rhythm was present. The jugulars showed a large systolic venous movement.

The chest was voluminous and physical signs of a hydrothorax were present, more marked on the right side.

The abdomen was distended in its upper half, due to the pressure of an enlarged smooth tender liver which reached downward almost to the level of the umbilicus. The spleen could not be palpated or outlined by percussion.

He had for two weeks or more after the onset of the attack a mild fever which ranged from 99° to 101° F. A leukocyte count, made during the second week of the illness, showed a leukocytosis of 13,000.

He died four days after my visit from the extreme cardiac insufficiency. No postmortem examination could be obtained.

CASE V.—Thrombosis of a coronary artery. (No autopsy.)

The following case was seen in consultation in July, 1917, at Arlington, Vt. Mr. D., aged sixty-two years, a railroad man, had for about two years been the subject of mild attacks of angina pectoris, manifested by pain of a constricting-like character, sub-

sternal in location and referred to the left shoulder and down the left arm in the ulnar distribution. He had been under a New York physician's care for hypertension and an enlarged heart.

Four days previous to my visit he was suddenly seized shortly after returning from a long automobile trip, he having driven his own car, with most excruciating substernal pain, great pallor and sensation of impending dissolution, which was only partially relieved by repeated doses of nitroglycerin and 0.5 gr. morphin hypodermically. Two days later, having in the interim suffered no precordial anxiety, he was taken with another similar attack to the above, although milder in character. Soon thereafter he became very dyspneic, was cyanosed, very nervous and restless and unable to sleep. His facial expression was pinched and he was very pale, with lips violaceous. His pulse, which before had been regular and slow at the rate of 68, with a systolic blood-pressure registering 190 mm., was now rapid and very irregular; his systolic pressure had dropped to 110 and his diastolic to 70. His heart action was tumultuous, and a soft systolic murmur was heard at the apex and faintly conducted to the left ("relative incompetency"). Many large subcrepitant rales were heard at the base posteriorly. My opinion was that following the onset of the second attack of angina pectoris a large branch of one of his coronary arteries became plugged with a thrombus and, accordingly, I gave a very grave prognosis.

I saw him two days later and found him in extremis with all the above-mentioned symptoms, greatly exaggerated, and, in addition, a localized fresh pericardial friction rub about 3 cm. in diameter, and heard best over the body of the right ventricle at the junction of the fourth costal cartilage with the sternum. He died the following day, and despite our entreaties no postmortem examination was allowed.

The interesting features of this case were the sudden onset, following a very severe anginoid attack, of grave myocardial insufficiency and auricular fibrillation, sudden fall of systolic blood-pressure, development of relative mitral incompetency and the sudden appearance of a transient localized pericardial friction rub.

CASE VI.—Thrombosis of a coronary artery with partial recovery; temporary loss of consciousness and disappearance of pulse at the wrist; localized bulging of heart shadow (roentgen-ray).

Mr. F. L., aged sixty-eight years, was a farmer by occupation.

History. His family history was without import. He had always been well since childhood, save that twelve years before he developed dizzy attacks, and it was then noted that his blood-pressure was high. Otherwise he had been very well and active on his farm.

The present illness began suddenly, June 28, 1922, when he

became very sick on his way to work in the fields. No acute pain was felt, but a feeling of sudden exhaustion and an inability to continue, with precordial distress and a numbness extending down the left arm and hand. When questioned closely he stated that there was no actual pain; just a numbness. This attack was accompanied with vomiting and a loose bowel movement. He was assisted to his home and laid on a couch, when he became very cyanosed and dyspneic and immediately lost consciousness. A physician was called and found him unconscious, very cyanosed and pulseless. Strychnin and nitroglycerin were administered and shortly afterward he improved. The pulse became palpable, with a rate of 40 per minute, but irregular in rhythm and volume (heart-block). He regained consciousness in a few seconds, and then complained bitterly of precordial distress, which was only partially relieved with 0.25 gr. morphin.

The next day his pulse-rate was 90; his temperature was 100° F. The day after this his pain was very much less; his pulse was very irregular and 140 per minute, weak and thready. The blood-pressure was 120/80 mm. His systolic pressure had previously been between 180 and 160 mm.

For a few hours only, on the third day following the attack, there was a pericardial friction rub heard over a small area to the left of the sternum near the junction of the left fourth costal cartilage. Improvement was very gradual for two weeks when there occurred a relapse, the pulse-rate reaching as high as 130, with periods of arrhythmia, extrasystoles and clinical alternation. This lasted about four days, when he suddenly improved, the pulse-rate not rising above 100 and quite regular.

At the present time, ten weeks after the onset of the trouble, the patient is up and about and feeling fairly well. He is quite dyspneic on exertion. The pulse remains about 90 and is, with the exception of extrasystoles, regular.

Fluoroscopic examination and roentgen-ray pictures show a well-defined localized bulging, apparently an aneurysmal dilatation, of the wall of the left ventricle at about its middle-third, the size of a small tangerine, or possibly a large dilated left auricle.

CASE VII.—Coronary artery thrombosis with sudden death. (No autopsy.)

W. A. B., aged fifty-six years, on April 21, 1921, had a severe crushing-like pain in the lower sternal and upper abdominal regions, which at first was thought to be due to an attack of indigestion or gall-bladder implication. This condition was suddenly followed by marked clinical evidences of myocardial insufficiency.

History. The family history was without import. He had always enjoyed good health, was a strenuous worker and had large business interests to occupy his attention.

When I saw him two days later, with Dr. Henning, the examination disclosed a well-nourished man with anxious facial expression, pale and ashen. The respirations were hurried and he evidently suffered from marked air-hunger. The pulse was rapid and very irregular. The cardiac impulse could not be seen or palpated. The heart sounds were clear but distant, the action tumultuous and numerous extrasystoles were easily recognized. The lungs were hyperresonant, except at the bases, which were dull, and many fine moist rales were present. There was soft edema of the feet and ankles. The blood-pressure was 135/110 mm. He was exceedingly nervous, and still complained of a continuous substernal pain of a dull character. So great was his distress that he was unable to rest in bed. Waves of dyspnea often appeared, accompanied with marked cyanosis.

From the above-described symptoms I made a probable diagnosis of coronary artery thrombosis, and advised Dr. Gow, the attending physician, to watch closely for the onset of a localized pericardial friction rub. I have, therefore, incorporated the notes contained in his recent letter to me.

I saw the patient, April 23, at which time he was unable to lie down and complained bitterly of severe substernal pain. The pain was only partially controlled by morphin (gr. $\frac{1}{8}$ every three hours). The heart sounds were very feeble and indistinct. There was no marked dyspnea, and at this visit no pericardial friction was heard. He remained the same for two days, when he developed a distinct pericardial friction rub over the body of the sternum near the xiphoid, which continued twenty-four hours and then disappeared. He then complained of no pain, was clear mentally and was able to lie comfortably. He seemed very weak, and stated that he was completely exhausted.

April 26 he seemed about the same, save that his pulse was very rapid.

April 27, just before death, he suddenly became unconscious and died in a few minutes. Digitalis was administered both *per oris* and hypodermically, without the slightest effect on the pulse. He evidently suffered from a thrombosis of a large branch of a coronary artery, and his death may possibly have been due to hemopericardium from a rent of the myocardial wall.

CASE VIII.—Coronary artery thrombosis with recovery.

Miss M. L., aged fifty-two years.

History. Her father died of cerebral hemorrhage; her mother died of mitral stenosis. Two brothers and one sister are healthy. One sister died in infancy of an unknown cause.

She had pneumonia seven years ago and jaundice twenty years ago, and has had vague rheumatic pains in the right hip-joint. For the past several weeks she has been conscious of shortness of

breath and substernal pain on exertion. During the past three years she has had three attacks of severe neuralgic-like pain in the sternal region which did not radiate.

In the evening of April 14, 1921, she had a sudden severe attack of substernal pain, with a sensation of severe pressure, as if the sternum was being pressed inward; this discomfort was accompanied by severe air-hunger. The pain at first radiated to the left wrist and later to the right. Her breathing was so difficult that when Dr. Russell called he found her in extremis, lying with her head out of a window. She was coughing up quantities of a light foamy blood-stained fluid. The pulse was very feeble, rapid and irregular. Her color was pale and her expression very anxious; the eyes were glassy and prominent.

I saw her the next morning and made the following notes:

Examination. A large well-built female, found lying down. Her respirations were quickened, her lips cyanosed and she had a loose wheezy cough, but no edema. Her chest was voluminous and emphysematous in type. The percussion note was hyperresonant, and there were many sonorous, sibilant and fine mucus rales, with puerile breathing.

Cardiovascular system: The radial pulse was small and irregular, with a rate of 120, and of fair tension. Both temporals and radials were tortuous and thickened, and there was an occasional extra-beat. The impulse was in the fifth interspace 1 cm. to the left of the left mid-clavicular line, a diffuse feeble tap. Cardiac dulness at the fourth rib extends from 2 cm. to the right of the sternum to 1 cm. to the left of the left mid-clavicular line. The rate at the apex was 144, and a definite gallop existed. The sounds were distant and very feeble. A soft systolic apical murmur, well-conducted to the left axilla, was heard, and a to-and-fro pericardial friction rub was well heard over the body of the sternum and strictly localized. The jugulars were full and pulsating and very difficult to count. The blood-pressure was 180/120 mm.

The liver dulness extended from the fifth rib to the costal border, and no pulsation of it was felt. The spleen was not outlined by percussion or palpation. The gall-bladder was not palpable, and no tenderness was observed. Her mind was clear, but she was very nervous and apprehensive.

The urine examined by Dr. Russell was found to be normal.

A diagnosis of thrombosis of a coronary artery was made by Dr. Russell, which seemed justifiable in view of the above-described symptom and physical findings. The pericardial friction was very distinct and strictly localized to an area about 2 cm. in diameter.

A note from Dr. Russell states that the patient was confined to her bed for four weeks, when she showed marked improvement; she was then permitted to be about her room, to walk slowly on the flat, and to do light work about the house. She has remained

in fair health, although when overtired or strenuous she has precordial distress and dyspnea.

CASE IX.—Thrombosis of a coronary artery with death three weeks later from myocardial insufficiency. (No autopsy.)

Mr. A., aged sixty-six years, was seen by me on September 21, 1921, in consultation with Dr. Gillen, of Cohoes, N. Y. Three days previously he had been seized suddenly at night with an excruciating pain, which was felt beneath the body of the sternum and passed directly through to the back. This pain lasted almost unabated for an hour and then was only partially relieved by a hypodermic injection of $\frac{1}{2}$ gr. of morphin. The pain gradually subsided, so that the next day he had no pain, but felt sore in the precordial region. For several months prior to the above-described attack he had noticed that on hurrying, walking against a strong wind, lifting heavily or going up stairs he felt a substernal pain and constriction of the chest. This condition had been diagnosed by the former attendant as one of indigestion.

Examination. The patient was propped up in bed with pillows. His facial expression was pinched and anxious and he was very pale. His lips were blue. The respiration was short and rapid, and he had an unproductive cough. He seemed very ill indeed. The pulse-rate was 140, very irregular and thready. The temporal and radial arteries were thickened, and he had a marked arcus senilis. The systolic pressure was 110 mm.; the diastolic pressure was 90 mm. The chest was universally vesiculotympanic on percussion, and a number of medium-sized bubbling rales were detected at the bases both in front and back. The heart action was tumultuously irregular; the impulse was a diffuse feeble tap in the fifth interspace, 0.5 cm. to the left of the left mid-clavicular line. The heart sounds were very distant. There was a slight though definite pericardial friction rub, best heard just inside of the impulse, close to the left edge of the sternum. The temperature was 100° F.

A diagnosis of thrombosis of a coronary artery was made (probably a branch of the right coronary), and in view of the physical findings of marked myocardial insufficiency a grave prognosis was given.

The patient continued the same for a period of about three weeks, when he developed edema of the extremities, marked oliguria, a very large, easily palpable and tender liver, great ascites and hydrothorax. He died suddenly a few days afterward. No post-mortem examination could be obtained.

CASE X.—Thrombosis of a small branch of a coronary artery with recovery.

Dr. E. E., a practising physician, entered the Samaritan Hospital,

October 29, 1921, complaining of extreme weakness, palpitation, some dyspnea and fainting and dizzy attacks on the slightest exertion.

History. His present illness began about five weeks before, while on a visit to Washington. It followed a rather hearty breakfast, the patient being suddenly seized with a severe pain beneath the lower sternal region. He vomited several times, and the pain was so severe that he took nitroglycerin and a hypodermic of morphin, with, after a time, considerable relief; he remained in bed for ten days, during which time his temperature ranged from 99° to 101° F. He stated that directly following the onset of the attack he was extremely prostrated and nervous.

His family history was unimportant. His personal history was also without special interest. Six years ago he was operated upon for adenoma of both breasts. Two years later he suffered from a nervous breakdown, from which he made an excellent recovery.

Examination. He was well nourished, presented no edema or cyanosis and when recumbent suffered from no shortness of breath. The skin and mucous surfaces were rather pale. His facial expression was anxious.

The chest was symmetric and expanded equally; the note was a little hyperresonant, but a good vesicular murmur existed throughout; no rales were detectable.

Heart: The impulse was palpable in the fifth interspace just within the left mid clavicular line; it was a rather feeble tap. The cardiac dulness began at the upper border of the fourth rib and extended 10 cm. to the left and 2 cm. to the right of the mid-sternum. No thrill or friction was detectable. The heart sounds were clear, but distant and quite feeble. There was no marked accentuation of either the aortic or pulmonic second sound and no adventitious sounds. The substernal dulness was not well outlined. No episternal pulsation was found. There was a definite, though slight, protodiastolic gallop rhythm; immediately on sitting upright in bed or in the standing position there appeared on auscultation an extrasystole following each normal beat, and this was also palpable at the wrist. On again assuming recumbency the extrasystole continued for a time and then disappeared to reappear on exertion. The rate at the wrist and apex in recumbency was 88. The blood-pressure was 125/80 mm. He stated that his usual systolic pressure was 165. Electrocardiograms showed typical ventricular extrasystoles, apical in character, with slight arborization block.

The abdomen was symmetric, soft and not distended. It contained no free fluid or tumor mass; no muscle spasms or herniæ existed. The liver dulness was normal, and the lower border was smooth and not tender. The spleen was not outlined, and the kidneys were not palpable. The rectum was normal. The neuromuscular system was negative.

The blood examination showed the red cell count to be 5,080,000; the leukocyte count was 12,000. The Wassermann reaction was negative.

The urinary examination showed nothing abnormal.

After six weeks in the hospital the patient showed a slight improvement. The extrasystolic arrhythmia continued, however, for more than six months after he left the hospital. The blood-pressure rose from 125 to 140 (systolic), but the diastolic pressure remained constantly at 80. He stated positively that he never previous to this attack had suffered from extrasystoles. I visited him recently and found him able to attend to office work. He stated that he felt splendidly and that he had had no cardiac embarrassment or pain.

From the history of the onset of his present illness, the severe substernal pain, the fever which lasted about ten days, the great asthenia, the feeble and distant heart sounds, the presystolic gallop rhythm, the extrasystoles occurring for a number of weeks after each normal beat (continuous bigeminy), the low blood-pressure, despite the absence, when first observed, of a pericardial friction rub and the fact that the above-mentioned symptoms came on directly after the onset of a sudden attack of what had been diagnosed as acute indigestion—all these indications led to the diagnosis of a probable thrombosis of a small branch of a coronary artery.

CASE XI.—Thrombosis probably of the right coronary artery, followed by a pulmonary infarct and a cerebral embolism, with right-sided hemiparesis and aphasia. Death. (No autopsy.)

The patient, Mr. P. W., aged sixty-six years, was seen by me on November 30, 1920, in consultation with Dr. Russell, of Arlington, Vt.

History. The family history was unimportant. The patient had been a sufferer from asthma for nine years. Three years before he developed a large prostate gland, which caused some difficulty in properly emptying his bladder, otherwise he had enjoyed good health until the onset of the present illness. He denied having had any venereal disease.

The present illness began November 27, 1920, with a pain of a boring squeezing-like character in the region of the cardiac impulse, which immediately passed to the mid-sternum. It continued almost uninterruptedly for three days. He ascribed it to the presence of gas, as he seemed very flatulent and distended. Suddenly at 6.00 A.M., November 30, he had another attack of a most agonizing character, beginning as above described and shooting across the chest to the right arm, into both sides of the neck and to the lower jaw. He was visited immediately by Dr. Russell, who found him very pale, with pinched, ashen-gray features,

bedewed with sweat, anxious facial expression and evidently in great anguish, with fear of impending death ("angor animi"). His radial pulse was rapid, feeble, very irregular and difficult to count. The vessel wall was definitely thickened.

It required $\frac{1}{2}$ gr. of morphin and several doses of glonoin to give him any relief. A few hours later he became very short of breath, cyanosed, had a sharp pain of stabbing-like character in the right chest below the angle of the right scapula, and coughed up some bright pink blood. Dr. Russell found his heart tumultuous and very irregular; the heart sounds distant and feeble, but no friction or endocardial murmur were present. Many fine moist rales at the bases posteriorly were detected.

I saw him at 8.00 P.M. of the same day and found his condition exactly as described by Dr. Russell. No pericardial friction was then heard, but near the angle of the right scapula a definite localized, superficial pleuritic friction rub was discovered and a few subcrepitant rales (pulmonary infarct).

The patient was so shocked and prostrated that the slightest exertion necessary to make the usual physical examination was attended with faintness and marked dyspnea. The blood-pressure was 110/90 mm.

From this history, symptoms and physical signs Dr. Russell had made a probable diagnosis of coronary artery occlusion. In this diagnosis I concurred and believed, because of the evidence of a pulmonary infarct coming so directly after the onset of a severe attack of angina pectoris, that a branch of the right coronary artery was probably the one plugged.

I advised the doctor to watch closely for the onset of a pericardial friction rub. This he did and was rewarded the following day by finding just above the xiphoid cartilage, and over the body of the sternum, a loud pericardial rub, covering an area about the size of a silver dollar.

He continued about the same, with much precordial distress, until December 6, when he was suddenly seized with a temporary loss of consciousness, right facial and lingual paralysis and incomplete motor aphasia and agraphia. I visited him again in the evening of the same day and found him conscious, but drowsy and unable to write or to say only a few words. His tongue deviated to the right and he had a lower right facial paralysis. The grasp of the right hand was also weak. These cerebral symptoms were thought to be due to an embolus dislodged from the left auricle or its appendix. He had from the onset of his illness a continuous temperature, never reaching higher than 101° F.

The patient lived but three weeks, and died of myocardial insufficiency. The pericardial rub lasted but forty-eight hours. No autopsy was permitted.

CASE XII.—Thrombosis of a coronary artery with loud pericardial friction heard over the entire precordium. Recovery.

E. K., aged seventy-seven years, married, was born in Germany.

History. He had always had good health and very moderate in his habits as to tobacco and alcohol. About twelve years before he had had an attack of pain in his chest, which was very severe and similar in character to the present one. He had had several severe attacks since then. He was the manager of a decorative firm, and always did more mental work than physical.

On February 1, at 10.00 A.M., while chopping wood in the basement of his house, he was seized with a severe pain in the chest, which caused him to fall to the floor. I saw him about 10.30 A.M. and found the following conditions: He complained of severe precordial pain and a sensation of pressure which was very severe. The pain extended down the left arm to the wrist. He was very pale; his pulse and heart rhythm were regular. There was a soft, systolic murmur heard at the apex and conducted toward the axilla. The systolic pressure was 160 mm.; the diastolic pressure was 120 mm. The arteries were very much thickened. It was necessary to give morphin to control the pain.

Late the next day there was a doubtful pericardial friction rub, inconstant and heard more distinctly to the right of the apex toward the xiphoid. Twenty-four hours later this rub was much louder and heard over the entire precordium. This intense rub, however, disappeared after a few hours, but could still be heard in the position where first heard. The cardiac rhythm was regular. During the next two or three days there was a slight return of precordial pain.

On February 3 the systolic pressure was 120 mm.; the diastolic pressure was 84 mm. The rhythm was regular. The heart sounds were feeble. The systolic apical murmur was quite indistinct, and the friction rub almost imperceptible. The bowels were very constipated. A mild delirium was present. The temperature had ranged from 90° to 100.5° F. The urine examination showed a specific gravity of 1030, an acid reaction, no albumin, sugar, bile or blood.

February 4 the systolic pressure was 110 mm.; the diastolic pressure was 68 mm. The friction rub was inaudible.

February 6 the systolic pressure was 120 mm. The rhythm was regular, and the heart sounds more distinct. A systolic murmur was distinctly heard.

On March 2 the patient was suddenly seized with a pain in the right side, and respiration became very painful. A very irritable cough developed and he expectorated dark red blood. A friction rub was heard over a small area at the base of the right lung anteriorly. Symptoms disappeared in ten days, only to recur a few days later with physical signs at the base of the right lung posteriorly.

These subjective symptoms and physical signs were thought to be due to a pulmonary infarct. He eventually made a fairly good recovery.

CASE XIII.—Coronary artery thrombosis with recovery.

Mrs. H., aged fifty-eight years, a dressmaker, married, was seen by me on February 24, 1922, in consultation with Dr. Johnson, of Troy, N. Y.

History. She had had four living children, no miscarriages and an uneventful menopause at fifty years of age.

On February 21 she was seized with an excruciating substernal pain of a crushing-like nature, accompanied with a sensation of impending dissolution. The pain did not radiate, but continued beneath the body of the sternum, as if the sternum was being crushed in against the spine.

Dr. Johnson gave her $\frac{1}{4}$ gr. of morphin, $\frac{1}{25}$ gr. of glonoin and several doses of codein; but despite this medication, the pain continued through the day and most of the night and then gradually disappeared. She stated that she had had four similar attacks of short duration, otherwise she had enjoyed good health. Physical examination showed a slightly built, somewhat emaciated female, with flushed face and no edema, cyanosis or dyspnea. The radial arteries were decidedly thickened, but easily compressed. The pulse was rapid and regular; the rate was 160. The blood-pressure was 125/100 mm. With a stop-watch a jugular pulsation of 320 per minute was counted, doubtless the auricles were in a state of acute flutter.

The heart sounds were feeble and distant; a slight systolic murmur over the body of the heart was present; a distinct, though faint, to-and-fro pericardial friction sound was plainly audible just above the region of the xiphoid cartilage, as if fast fading away.

Dr. Johnson stated that two days previously the pericardial friction rub was very loud, and that he had followed it as it had gradually faded and disappeared. Fine rales were present at the bases. The chest was hyperresonant throughout. The urine showed a definite trace of albumin and hyalin and granular casts. Its specific gravity was 1022 and the quantity diminished. There was no rise of temperature. A blood count was not done. Digitalis was given in large doses without the slightest effect on the cardiac rate. The tachycardia continued for a period of several weeks, when it gradually diminished. She slowly improved, and in six weeks was able to be up and about, to walk on the level and to do light housework without embarrassment. At present she appears well, although overexertion brings on faintness and substernal pain.

From the symptom of severe angina pectoris, the sudden onset of acute auricular flutter, low systolic blood-pressure, narrow pulse

pressure, acute myocardial insufficiency and a very definite localized pericardial friction rub, there could be but little doubt of the correctness of the diagnosis of thrombosis of a branch of a coronary artery. In view of her great improvement and apparent recovery, it is probable that but a small branch could have been plugged.

Summary. The following is a summary of the salient features of this interesting symptom complex:

1. Sudden severe anginoid pain, substernal or upper abdominal.
2. A pinched ashen-gray or very pale facies, often associated with the sensation of impending dissolution.
3. An acute emphysematous distention of the lungs, with dyspnea or extreme orthopnea and moist crackling rales at the bases of the lung, together with the evidences of the acute onset of cardiac decompensation.
4. An easily compressed rapid thready pulse, which may present almost any form of arrhythmia.
5. A sudden drop in the systolic pressure following the severe pain and early myocardial exhaustion.
6. A cardiac impulse, if palpable, that is a diffuse feeble tap, distant heart sounds and often a tic-tac or gallop rhythm.
7. A localized pericardial friction rub, which is evanescent, appearing as early as a few hours or a day or two after the sudden onset of the agonizing pain. It may be missed if the infarct involves the posterior aspect of the heart.
8. A fever of short duration and of a mild type associated with a polymorphonuclear leukocytosis. This does not occur in simple angina pectoris.
9. Inversion or iso-electric position of the T-wave, with arborization block.
10. Associated with the above described symptoms, the presence of a large tender liver, together with the symptoms and physical signs of pulmonary infarction, is suggestive of thrombosis of the right coronary artery or its branches, while the sudden onset of pulmonary edema or recurring attacks, together with the development of sudden arterial plugging of the vessels of the brain, viscera or extremities, with the characteristic electrocardiogram is highly suggestive of a thrombosis of a branch of the left coronary artery.

REFERENCES.

- Acker, R. B.: Delayed Death in Coronary Thrombosis, *Jour. Am. Med. Assn.*, 1919, 73, 1692.
- Allbutt, Sir Clifford: Diseases of the Arteries including Angina Pectoris, 1915, 2, 450.
- Blumer, George: Coronary Thrombosis, *Albany Med. Ann.*, 1922, 43, 288.
- Gross, Louis: The Blood Supply to the Heart in its Anatomical and Clinical Aspects, New York, Hoeber, 1921.
- Gorham, L. W.: Significance of Transient Localized Pericardial Friction in Coronary Thrombosis, *Albany Med. Ann.*, 1920, 41, 109.
- Gorham, L. W.: Diseases of the Heart Simulating the Picture of an Acute Surgical Condition of the Abdomen, *Albany Med. Ann.*, 1922, 43, 157.

- Herrick, J. B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, *Jour. Am. Med. Assn.*, 1912, **59**, 2015.
- Herrick, J. B.: Thrombosis of the Coronary Arteries, *Jour. Am. Med. Assn.*, 1919, **72**, 387; *Jour. Michigan State Med. Soc.*, 1919, **18**, 49.
- Herrick, J. B.: Concerning Thrombosis of the Coronary Arteries, *Trans. Assn. Am. Phys.*, 1918, **33**, 408.
- Herrmann, G. R.: Thrombosis of the Coronary Arteries with Tachycardia, *Jour. Missouri State Med. Assn.*, 1920, **17**, 406.
- Kahn, Morris: Electrocardiographical Signs of Coronary Thrombosis and Aneurysm of Left Ventricle of Heart, *Boston Med. and Surg. Jour.*, 1922, **187**, 788.
- Krehl: Die Verschluss der Kranzarterien, *Nothnagel's System*, **15**, 108.
- Libman, E.: Some Observations on Thrombosis of the Coronary Arteries, *Trans. Assn. Am. Phys.*, 1919, **34**, 138.
- Longcope, W. T.: The Effect of Occlusion of the Coronary Arteries on the Heart's Action and its Relationship to Angina Pectoris, *Illinois Med. Jour.*, 1922, **41**, 186; *Wisconsin Med. Jour.*, 1922, **20**, 449; *Jour. Iowa Med. Soc.*, 1922, **12**, 314.
- Osler: *Lectures on Angina Pectoris and Allied States*, Appleton, 1897.
- Porter, W. T.: Further Researches on the Closure of the Coronary Arteries, *Jour. Exp. Med.*, 1896, **1**, 46.
- Porter, W. T.: On the Results of Ligation of the Coronary Arteries, *Jour. Physiol.*, 1894, **15**, 121.
- Paullin, J. E.: Thrombosis of the Coronary Arteries, *South. Med. Jour.*, 1921, **14**, 16.
- Robinson, G. C., and Herrmann, G. R.: Paroxysmal Tachycardia of Ventricular Origin and its Relation to Coronary Thrombosis, *Trans. Assn. Am. Phys.*, 1920, **35**, 155.
- Smith, F. M.: The Ligature of the Coronary Arteries, *Arch. Int. Med.*, 1918, **22**, 8.
- Sternberg, M.: Pericarditis Epistenocardica, *Wien. med. Wchnschr.*, 1910, **60**, 14.
- Wearn, J. T.: Thrombosis of the Coronary Arteries with Infarction of the Heart, *AM. JOUR. MED. SCI.*, 1923, **165**, 250.

A COMPARATIVE STUDY IN DIGIFOLIN ADMINISTRATION.*

BY NORMAN E. CLARKE, M.D.,

DETROIT, MICH.

(From the Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Mich.)

THE first scientific work on digitalis therapy was published by Withering¹ in 1785. Interest in this important contribution to medical science was allowed to lapse until revived by McKenzie during the present generation. Since McKenzie's early work with digitalis numerous investigators have added to our knowledge of the properties, administration and usefulness of this drug. At present digitalis is the most useful drug for the treatment of heart disease.

The early preparations of digitalis were the infusion, tincture and the powdered leaves. It was soon recognized that some cases of acute cardiac decompensation required intensive treatment by other than oral administration. Because of unfavorable properties these early pharmaceutical compounds were unsatisfactory for other than oral therapy. Attempts were made to give the tincture

* I wish to express my appreciation to Dr. F. N. Wilson for his many kind and helpful suggestions during the preparation of this paper.

or infusion by rectum. However, these original preparations caused excessive irritation to the rectal mucosa and it was impossible to have the required amount retained.

One of the first water-soluble preparations suitable for other than oral administration was digalen. According to Wolfer,² Naunyn was the first to give this preparation intravenously. This method of administration was further investigated by Naunyn's pupil, Kottmann.³ This investigator claimed that the reaction was almost instantaneous, and that within a few minutes the maximum effect of the drug was manifested in hearts still retaining reserve power. Kottmann based his claims on: (1) An increase in the strength of the pulse and heart-beat; (2) elevation of the blood-pressure; (3) improvement in the patient's general condition; (4) a diuresis.

Fraenkel⁴ introduced intravenous administration of strophanthin for the treatment of heart disease. His original maximum dose was 1 mg., from which several fatalities occurred. The giving of this powerful drug, which occasionally caused death, has fortunately tended to limit promiscuous intravenous digitalis therapy. It has created in many a fear of digitalis administration intravenously and impressed the necessity of carefully considering the therapeutic problem in each case.

There are numerous methods for administering digitalis. Besides the oral and intravenous methods, intramuscular and subcutaneous injections are used and recently rectal insertion has been revived. The present popularity of intravenous therapy is reflected in the variety of digitalis preparations. This condition has been fostered by pharmaceutical houses who enthusiastically exploit the virtues and advantages of their refined preparations. There is little accurate information in support of these claims.

Recently Meyer⁵ reported excellent results with rectal administration of dilute tincture of digitalis in certain types of heart disease. In some types of heart failure, other than oral therapy is advantageous to the patient. The giving of digitalis by other than oral administration is, however, rarely necessary or justifiable.

The reasons for administering digitalis by other than the oral method fall mainly into three general groups: (1) The avoidance of irritative gastric symptoms; (2) the unknown factor of absorption from the gastro-intestinal tract; (3) the securing of more prompt and efficient action.

The emetic action of digitalis has been recognized since the time of Withering. Early numerous discrepancies were noted in the deductions from animal experiments and the occurrence of gastric symptoms in patients receiving digitalis therapeutically. It remained for Hatcher and Weiss⁶ to demonstrate fully the mechanism of the central emetic action of this drug. They have shown the primary action of digitalis to be on the heart muscle. To produce emesis the nervous connections between the heart and the vomiting center must be intact. This important investigation has

tended to make us lose sight of the fact that there is a direct irritating effect on the gastric mucosa which induces vomiting. The direct action occurs more frequently in patients severely ill or in acute decompensation when the tendency to vomiting is already present. The central emetic action is a delayed and cumulative manifestation of the drug. The direct action occurs after the first dose and shortly after the entrance of the drug into the stomach. Meyer⁵ found that emesis was not always due to central stimulation, and he states that by comparison of oral, intravenous and rectal administration he finds that it is not as frequent as supposed.

The principal advantage of modern digitalis preparations is their lessened irritating property. Meyer frequently had patients request digipuratum instead of tincture of digitalis, because it was less irritating to the stomach.

The variability in absorption of different digitalis preparations from the gastro-intestinal tract has frequently been noted. The degree of cardiac decompensation also affects the absorption of drugs. Wolfer² found poor absorption after oral administration in cases in which there was congestion of the liver. Meyer⁵ likewise noticed lessened absorption from the upper gastro-intestinal tract when hepatic congestion was present while absorption from the lower bowel was undiminished, as he demonstrated by rectal administration. This variation in absorption is due to different venous drainage. The upper gastro-intestinal tract is drained entirely through the liver by the portal system. The rectal venous return is through the hemorrhoidal superior, middle and inferior veins. The superior and medial veins enter the portal system. The inferior vein goes direct to the abdominal vena cava. The draining of part of the blood from the rectum direct to the central collecting system permits drugs readily to reach the heart when liver congestion delays absorption from the upper gastro-intestinal tract. Luthje⁷ has also demonstrated this difference in absorption from the upper and lower bowel by the use of glucose in diabetic patients. In two standardized tinctures of digitalis, given by mouth, Wedd⁸ found a decided difference in absorption as measured by electrocardiographical changes. Eggleston and Wyckoff,⁹ however, after an extensive study of this question, concluded that the factor of absorption is of sufficient uniformity with good galenical preparations to permit the establishment of an average total therapeutic requirement. This conclusion is confirmed in the work of Pardee¹⁰ and Robinson.¹¹ The amount necessary by oral administration for complete digitalization on the basis of body weight apparently may be fairly accurately determined. The rapidity of absorption must, however, depend on the degree of cardiac decompensation and congestion.

We have tried to determine more accurately the variation in rapidity and efficiency of action of the same digitalis preparation given by different methods. The rapid and efficient action of

strophanthin intravenously is sufficiently well known to require no comment. The poor action of strophanthin given by mouth is due to its poor absorption from the gastro-intestinal tract. Cohn and Levy¹² have compared the action of digipuratum by mouth and strophanthin intravenously in patients with auricular fibrillation. The two drugs were given in divided doses, and in most cases the periods of administration were the same. By electrocardiographical changes they noted that the effect of strophanthin intravenously in divided doses may not be noted for two hours. Digipuratum by mouth in divided doses may cause changes in a little more than two hours. The strophanthin action rarely lasted more than five days while digipuratum effects lasted usually ten days and as long as twenty-three days. Strophanthin caused but slight and transient changes in the T-wave of the electrocardiogram, while digipuratum caused striking and prolonged effects. Morris¹³ gave dilute tincture and infusion of digitalis intravenously and obtained immediate action with no harmful secondary results. He has failed to give records of his experiments, so his work is not suitable for comparison. Fulton¹⁴ found definite reduction in the heart-rate six to eight hours after intravenous administration of strophanthin, but does not state dosage or time intervals. Pratt¹⁵ noted striking benefit with intravenous amorphous strophanthin in cases of heart failure with regular cardiac rhythm, when the patients had failed to respond to digitalis by mouth. This observation is unusual in view of the accepted belief of the mutually interchangeable action of the various bodies.

Methods of Investigation. Patients with auricular fibrillation comprise about two-thirds of our cases. The recorded results are from 25 patients, 10 of whom could not be used in their entirety because of death, defective records or some other mishap. The hearts were in varying stages of decompensation, and no effort was made at selection. All patients were confined strictly to bed and maintained on the usual low protein, low caloric diet throughout the entire period. Patients with edema were limited to 1500 cc of fluid daily. Morphin was used as a sedative, but no other medication was permitted. The ampoule form of digifolin was used in all cases. After some preliminary work the dose chosen was 5 ampoules (0.5 gm. of standardized digitalis leaf), given twice daily. The interval between doses was in most cases twelve hours, as Pardee has shown that the maximum effect is obtained in about six hours, and that intervals of twelve to eighteen hours are best in order to allow early toxic signs to manifest themselves. Two electrocardiograms were taken daily, usually about six hours after administration. All electrocardiograms, including the control curve, were taken with the patients in bed.

Effect on Heart-rate. One of the most characteristic effects of digitalis on auricular fibrillation is slowing of the rate. As digifolin (5 ampoules) was given twice daily, the apex-rate was counted every

five, or in a few cases, every ten minutes thereafter for two hours, then every half hour for four hours and every hour for the following six hours.

The accuracy of the counts was carefully supervised. In patients with auricular fibrillation a preliminary sudden fall in heart-rate was noted within the first twenty minutes following the intravenous injection of the drug. This fall in heart-rate was not of sufficient degree or frequency to allow us to draw any definite conclusions. The results are given in Table I. The period of maximum slowing was considered as that point on the chart at which the apex count showed the greatest decrease in rate below that at the time of administration. A decrease of less than 10 beats has not been considered significant.

TABLE I.—EFFECT OF DIGITALIS ON THE HEART-RATE WHEN ADMINISTERED BY DIFFERENT METHODS.

Method.	Intravenous.	Intramuscular.	Mouth.
Earliest noted maximum slowing	1 hr.	1 hr. 30 min.	2 hrs. 45 min.
Average time that maximum slowing was noted	3 hrs. 50 min.	4 hrs.	6 hrs.
Latest noted maximum slowing	6 hrs.	6 hrs. 15 min.	11 hrs. 30 min.

The intravenous findings were obtained from 23 single administrations. The maximum slowing was noted within one hour or as late as six hours, but occurred on an average in three to four hours. In 28 intramuscular injections the maximum slowing was noted in one and a half hours or as late as six and a quarter hours, but it occurred at an average of four hours. The average time intervals required for obtaining maximum slowing of the heart-rate by divided doses of digifolin given intravenously or intramuscularly are approximately the same, intramuscular injection taking but a slightly longer time.

In oral administration the earliest maximum slowing occurred in two and three-quarters hours, the latest in eleven and a half hours and the average at about six hours. The average time period for maximum slowing of the heart-rate in oral administration compares favorably with that found by Pardee.¹⁰ In giving massive doses of digitalis by mouth Robinson¹¹ found the period for maximum slowing of the ventricular rate to be from two to five hours. It appears to take two or three hours longer to obtain maximum slowing of the heart-rate in auricular fibrillation by oral than by intravenous or intramuscular injection of digifolin when the drug is given under fixed conditions.

Comparative Efficiency as Measured by Digifolin Requirement. That we might compare the amount of digifolin causing the earliest changes and the full therapeutic effect on the heart in the three methods of administration, electrocardiograms were taken twice daily. The curve in most cases was taken about six hours after medication; in a few intervals of twelve hours elapsed. The early action of the drug on the heart was noted by changes in the T-wave.

This has been shown by Cohn, Frazer and Jamieson¹⁶ to be the earliest manifestation of digitalis action. They considered lowering or inversion of the T-wave, or an isoelectric T-wave, evidence of activity. They found that this change occurred in most cases before any gastro-intestinal symptoms were noted. Wedd⁸ found the earliest electrocardiographical change to be in the T-wave. Pardee¹⁰ found T-wave changes in from two to four hours after the oral administration of tincture of digitalis equal to 1 minim of tincture per pound of body weight. The maximum effect occurred in from six to seven hours.

The data were obtained from 15 unselected cases and are given in Table II. Many of these patients had auricular fibrillation, and a brief history of each is given. The following patients received digifolin intravenously:

Report of Cases. CASE I.—Miss I. R., aged forty years, had had frequent attacks of tonsillitis. Her first symptoms of cardiac weakness had occurred one and a half years previously. The heart was slightly enlarged. There was stenosis of the mitral valve, and auricular fibrillation was present. She was dyspneic and complained of palpitation. An associated toxic goiter complicated her illness.

CASE II.—Mr. C. L., aged fifty-five years, had an advanced arteriosclerosis, definite cardiac enlargement, auricular fibrillation and cirrhosis of the liver. He was dyspneic and had cyanosis, with edema of the feet and legs, and complained of palpitation and orthopnea.

CASE III.—Mr. D. H., aged forty-nine years, had had cardiac symptoms during the preceding year. He had advanced arteriosclerosis, cardiac enlargement and auricular fibrillation. He had cyanosis, was dyspneic and complained of gastric disturbances. There was a large collection of ascitic fluid and edema of both legs.

CASE IV.—Mrs. C. C., aged forty-five years, had had an attack of "rheumatic fever" at the age of fourteen years associated with symptoms of cardiac decompensation. A second attack of rheumatic fever occurred at the age of thirty-five years. She had mitral stenosis, enormous cardiac enlargement, auricular fibrillation, dyspnea, palpitation and edema.

CASE V.—Mr. E. F., aged forty-eight years, had had rheumatic fever at the age of twenty-three years and again at forty-four years. He had had frequent attacks of tonsillitis. His symptoms had appeared one year previously. He showed a moderate degree of arteriosclerosis, mitral stenosis, auricular fibrillation, moderate enlargement of the heart, cyanosis and dyspnea. He complained of palpitation.

The following patients received digifolin by mouth:

CASE VI.—The history of Miss I. R. is given under those who received intravenous therapy. Sufficient time elapsed between her two periods of digitalization to avoid any question of persistent digitalis action.

TABLE II. COMPARATIVE EFFICIENCY OF THE THREE METHODS OF ADMINISTRATION AS MEASURED BY DIGIFOLIN REQUIREMENT.

Patient.	Case No.	Method.	Weight, kg.	Amount digifolin at first E. K. G. change.	Cat unit per kg.	Digifolin for full therapeutic effect.	Cat unit per kg.	Reason drug was discontinued.	Change in patient's condition.
Miss I. R. . .	1	Intravenous	54.5	5	0.0600	20	0.2414	Slow apex-rate; nausea	Improved.
Mr. C. L. . .	2	Intravenous	70.4	5	0.0470	28	0.2640	Nausea-anorexia; slow apex-rate	Much improved.
Mr. D. H. . .	3	Intravenous	61.8	10	0.1064	20	0.2128	Bigeminal pulse	Much improved.
Mrs. C. C. . .	4	Intravenous	67.0	5	0.0490	25	0.2450	Slow apex-rate (52)	Improved.
Mr. E. F. . .	5	Intravenous	67.0	5	0.0490	20	0.2000	Slow rate; long pauses	Improved.
Average	0.0623	...	0.2326		
Miss I. R. . .	6	Mouth	53.6	10	0.1220	35	0.4350	Nausea; anorexia	Improved.
Miss L. B. . .	7	Mouth	39.0	10	0.1690	20	0.3380	Nausea; vomiting	Slight improvement.
Mrs. L. H. . .	8	Mouth	99.0	10	0.0664	20	0.1328	Slow apex-rate (42)	No change.
Mr. D. N. . .	9	Mouth	72.7	15	0.1370	45	0.4120	Rapid irregular pulse	Slightly improved.
Mr. W. L. . .	10	Mouth	68.0	10	0.0969	43	0.4150	Nausea; vomiting; prolonged pulse-rate	Improved.
Average	0.1182	...	0.3465		
Mr. W. N. . .	11	Intramuscular	78.1	5	0.0420	20	0.2520	Nausea; vomiting	Much improved.
Mr. I. W. . .	12	Intramuscular	77.0	10	0.0850	30	0.2550	Nausea; vomiting	Improved.
Mrs. M. K. . .	13	Intramuscular	84.0	5	0.0390	30	0.2346	Nausea; vomiting	Slightly improved.
Mr. A. F. . .	14	Intramuscular	91.0	10	0.0720	28	0.2030	Slow apex-rate; nausea	Improved.
Mr. C. H. . .	15	Intramuscular	93.0	10	0.0700	43	0.3080	Slow apex-rate; nausea	Much improved.
Average	0.0610	...	0.2505		

CASE VII.—Mrs. L. B., aged sixty-one years, had a history of rheumatic fever. The heart was slightly enlarged. Mitral stenosis was present with hypertension. An orthodiagram showed a wide dense aortic shadow; the Wassermann test of the blood was 4+. Slight signs of cardiac failure were present.

CASE VIII.—Mrs. L. H., aged fifty-nine years, was first admitted in 1918 for cardiac failure with auricular fibrillation. At the second admission, in October, 1922, she had a few cardiac symptoms. She showed slight arteriosclerosis, auricular fibrillation, moderate cardiac enlargement and no valvular lesions. There was a history of rheumatic fever at the age of sixteen years.

CASE IX.—Mr. D. N., aged sixty-four years, had an essentially negative past history. He had noticed slight dyspnea and palpitation on exertion for ten years. The acute condition had been present for nine weeks, with increasing dyspnea and palpitation. There was a large amount of edema in both legs. He showed advanced arteriosclerosis with moderate cardiac enlargement.

CASE X.—Mr. W. L., aged thirty-eight years, gave an indefinite history of rheumatic fever. He complained of dyspnea, palpitation and pain over the precordium and in the left side of his chest. A high grade of cyanosis and edema were present, with mitral stenosis, enormous cardiac enlargement, pulmonary congestion and clubbed fingers.

Digifolin was given by intramuscular injection in the following cases:

CASE XI.—Mr. W. N., aged fifty-three years, had a history of frequent ulcerative sore throats and syphilis. His Wassermann test was 4+. He showed an advanced arteriosclerosis, mitral stenosis, enormous cardiac enlargement, auricular fibrillation and aortitis. Intense cyanosis was present, also dyspnea and orthopnea with an extreme edema of his legs and swelling of the abdomen.

CASE XII.—Mr. I. W., aged sixty years, whose past history was essentially negative, had extreme swelling of the arms and legs with marked dyspnea and palpitation, advanced arteriosclerosis and enormous cardiac enlargement. The orthodiagram showed a dense aortic shadow. He had acute decompensation.

CASE XIII.—Mrs. M. K., aged thirty-five years, had had one attack of rheumatism and a severe puerperal infection six years previously. She also had a history of syphilis. The heart was enlarged, the neck veins engorged and aortitis with aortic regurgitation were present. There was stenosis of the mitral valve. Dyspnea and palpitation with slight edema of the legs were present.

CASE XIV.—Mr. A. F., aged fifty-seven years, had an essentially negative past history. He had extreme arteriosclerosis, cardiac enlargement, cirrhosis of the liver and auricular fibrillation. The left arm and leg were paralyzed as a result of a preceding "stroke."

He was dyspneic and had cyanosis with extreme edema of the lower half of his body. Palpitation was complained of, and severe mental deterioration was present.

CASE XV.—Mr. C. H., aged fifty-seven years, whose father and several brothers had died of "heart disease," had an advanced arteriosclerosis, cardiac and hepatic enlargement, engorged neck veins, auricular fibrillation, dyspnea, cyanosis and edema. The chief complaint was palpitation.

There was a wide variation in the patients' weight, with considerable difference in the amount of digifolin required to produce the earliest and maximum effects. Comparison has been made on the cat unit per kilogram basis.

For standardization of our digifolin we used the rapid digitalis-ouabain method of biological assay developed by Hatcher and Brody.¹⁷ Five cats were used, and 1.52 cc of the lot of digifolin used was found to equal 1 cat unit.

Considerable variation was found in the cat unit per kilogram required to initiate the first electrocardiographical changes. The average amount of digifolin required to induce the alteration in the T-wave was 0.0623 cat unit per 1 kg., by intravenous injection, 0.061 cat unit per 1 kg., by intramuscular injection, and 0.1182 cat unit per 1 kg., by oral administration. Intravenous and intramuscular injection are of equal efficiency in the amount of digifolin thereby required to produce early effect. By oral administration the drug appears about half as efficient.

The maximum activity was based on both clinical and electrocardiographical changes. In some the appearance of anorexia, nausea or vomiting were our indications of complete digitalization, while others were measured by a heart-rate below 60, bigeminal pulse or exaggerated electrocardiographic changes. A decided uniformity was noted in the patients who received digifolin intravenously. Among those receiving digifolin by mouth, the low figure of 0.1328 is noted for Case VIII. By intramuscular therapy an amount (0.308) considerably higher than the average was obtained for Case XV. These wide variations from the average were unusual, and we can offer no explanation for them. In intravenous and intramuscular injections the amount of digifolin necessary to produce the earliest noticeable effects and the full therapeutic effect is apparently almost the same. When the drug is administered by mouth it appears that it is about half as efficient in relation to the amount required to produce these same effects.

Comparative Efficiency as Noted by Time of Action. The question of the degree of efficiency, as denoted by the amount of digifolin per kilogram required for the three methods of administration has been stated. It remained to compare the three methods in relation to the average time required to produce earliest and maximum effects. Digifolin having been given twice daily at intervals of

twelve hours, two electrocardiograms were taken, in most cases, six hours following each administration of the drug. The period for the earliest effect is a measure of the time elapsing from the giving of the first dose of digifolin until the first change is noted in the T-wave of the electrocardiogram. The maximum time period is a measure of the time elapsing from the initial dose to the appearance of toxic symptoms as noted either clinically or electrocardiographically. The average cat unit per kilogram of body weight for the two periods has been taken from Table II.

We have not attempted to determine the actual time of the earliest and maximum effects on the heart, but rather to compare these changes as noted under fixed conditions for the three methods of administration.

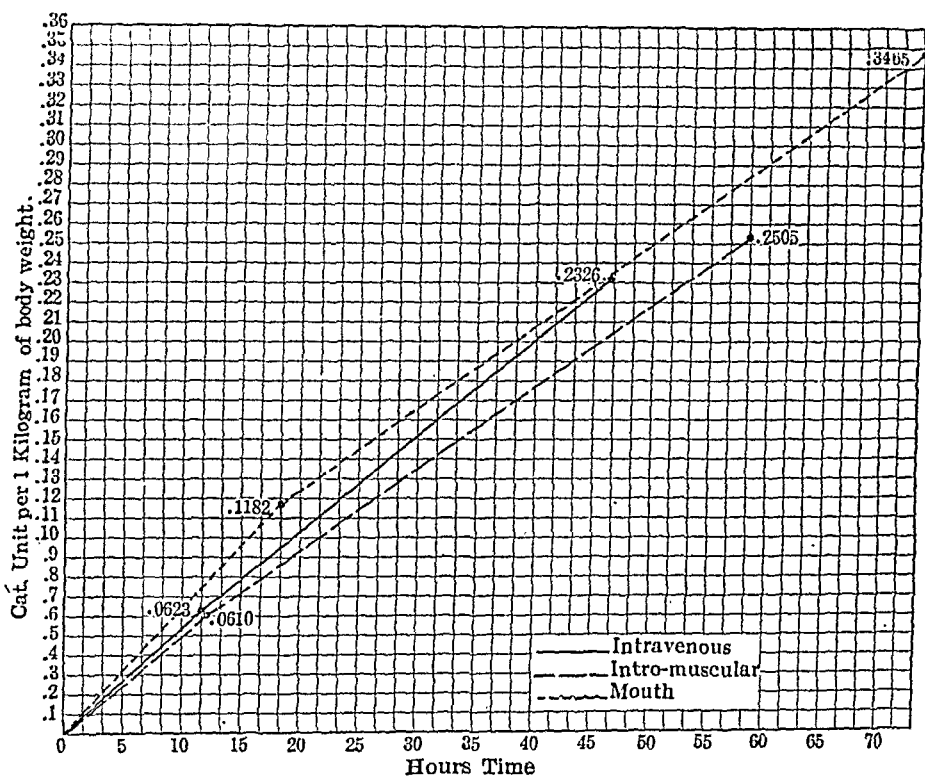


FIG. 1

The results in Fig. 1 demonstrate the superior comparative efficiency of intravenous digitalis therapy, both in rapidity of action and quantity of drug required. By this method activity was first noted at an average of ten and a half hours with digifolin equal to 0.0623 cat unit per 1 kg. of body weight. An average maximum activity occurred in forty-six hours with digifolin equaling 0.2326 cat unit per 1 kg. of body weight. Early effects by intramuscular injection were noted with 0.061 cat unit per 1 kg. of body weight, which is similar to the intravenous requirement. However, there was a slight delay in time, which had been previously noted in the slightly longer delay in slowing the pulse (Table I). This slight

delay, presumably due to slightly slower utilization, is apparently accentuated by succeeding doses, as the maximum effect is noted in about one-third longer time. The relative efficiency of intravenous and oral administration in the amount of drug per unit of body weight required has been previously discussed. In comparing the time intervals, we note that intravenous is almost twice as efficient an oral administration in producing early electrocardiographical changes. This same proportion holds approximately true in the production of the full therapeutic effect.

Unfavorable Results from Intravenous Administration of Digifolin. In Wolfer's paper, published in 1921, he states that he had never observed, and had been unable to find in the literature, the occurrence of unfavorable symptoms or death from digitalis given intravenously.

It was our unfortunate experience to observe 2 cases in our brief series in which the patients' deaths may possibly have been in part due to the administration of digifolin intravenously. A brief summary of each case is presented:

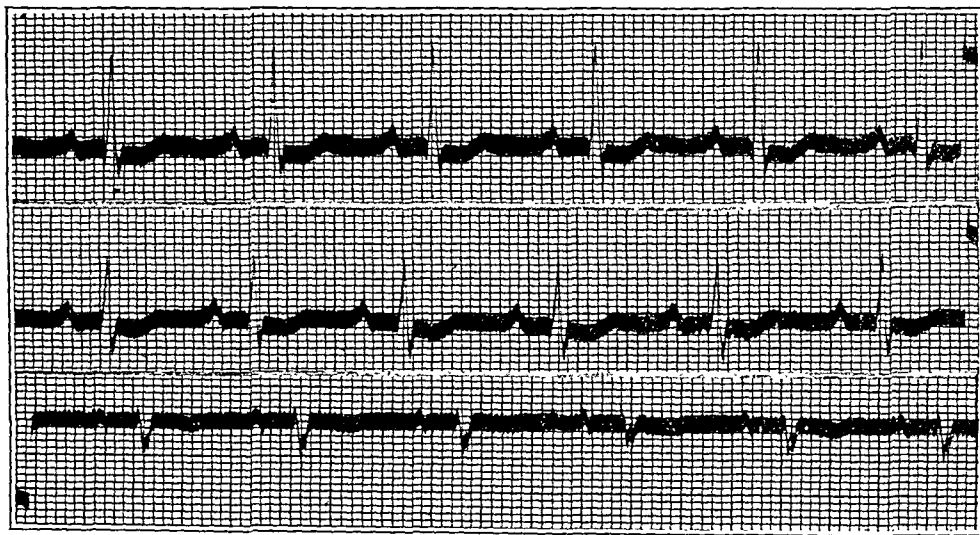


FIG. 2.—Miss A. M.: Leads I, II and III taken at admission. This showed only inversion of the T-waves in all three leads.

CASE XVI.—Miss A. M., aged fifty-three years, entered the University Hospital in a state of extreme cardiac decompensation. Her symptoms of dyspnea, palpitation, weakness and swelling of the legs and abdomen had been slowly but gradually increasing since an attack of rheumatic fever ten years previously. These symptoms had become acute during the last two months. She had spells, increasing in frequency and severity, of acute orthopnea, palpitation, a sense of suffocation in her chest and nausea with vomiting. At the time of admission there was extreme cyanosis. Examination revealed mitral stenosis, aortic regurgitation, enormous edema of both legs, with fluid in the chest and abdominal

cavities. She received 5 ampoules of digifolin intravenously at once and 20 ampoules in all over a period of forty-eight hours. An early digitalis effect was noted in the curve. One hour following the last administration the patient's condition appeared much improved, but the curve showed a complete auriculoventricular dissociation with variations in the position of the ventricular pacemaker. Another curve taken two hours later showed the same condition with numerous extrasystoles. Four hours after receiving the last dose of digifolin her pulse suddenly fell, and without warning respiration ceased.

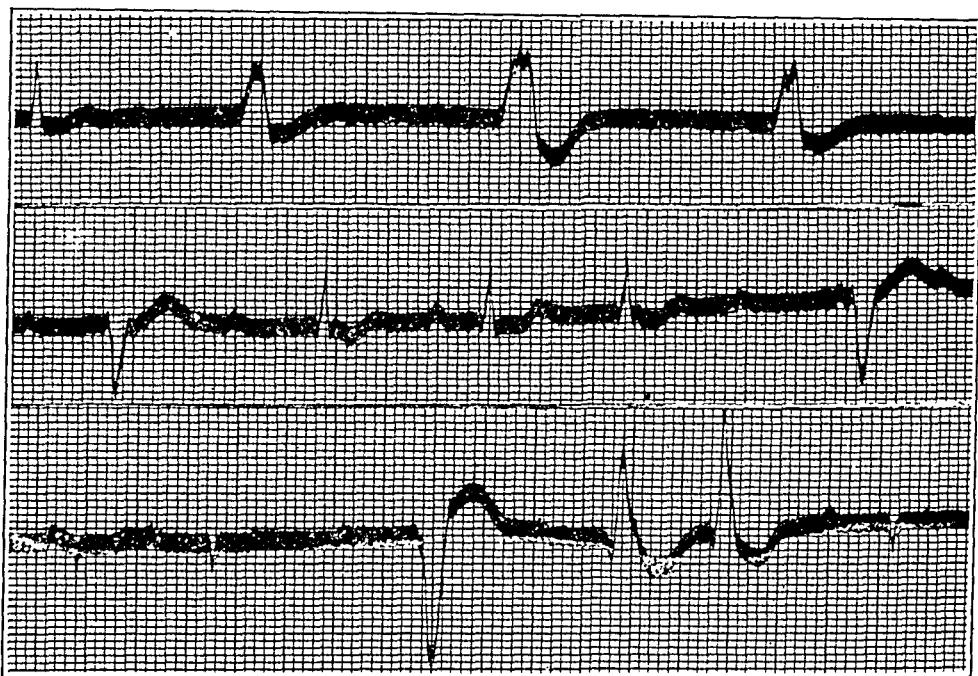


FIG. 2.—Miss A. M.: Leads I, II and III taken three hours before death, showing complete auriculoventricular dissociation, with variations in the position of the ventricular pacemaker.

CASE XVII.—Mr. W. W., aged seventy-one years, complained of dyspnea, orthopnea, weakness and insomnia. The cardiac condition had been present four years, becoming acute during the last six weeks. At entrance he had Cheyne-Stokes respirations, an enormously enlarged heart, but no murmurs. There were many extrasystoles, and the heart sounds were distant. The aortic second sound was much accentuated and well heard to the left of the sternum. The electrocardiogram showed a right bundle branch-block. The patient was given digifolin intravenously, 20 ampoules in all, in 5-ampoule doses twice daily. Following the last injection he appeared improved until suddenly, while conversing with his relatives, he fell backward gasping, extremely cyanosed, and the heart stopped beating. For several seconds after the heart sounds

had become inaudible a rapid fluttering movement was noticed in the external jugular vein on the right. An electrocardiogram taken on the day preceding death showed the same cardiac disturbance



FIG. 3.—Mr. W. W.: Leads I, II and III taken shortly after admission, showing a right bundle-branch block.

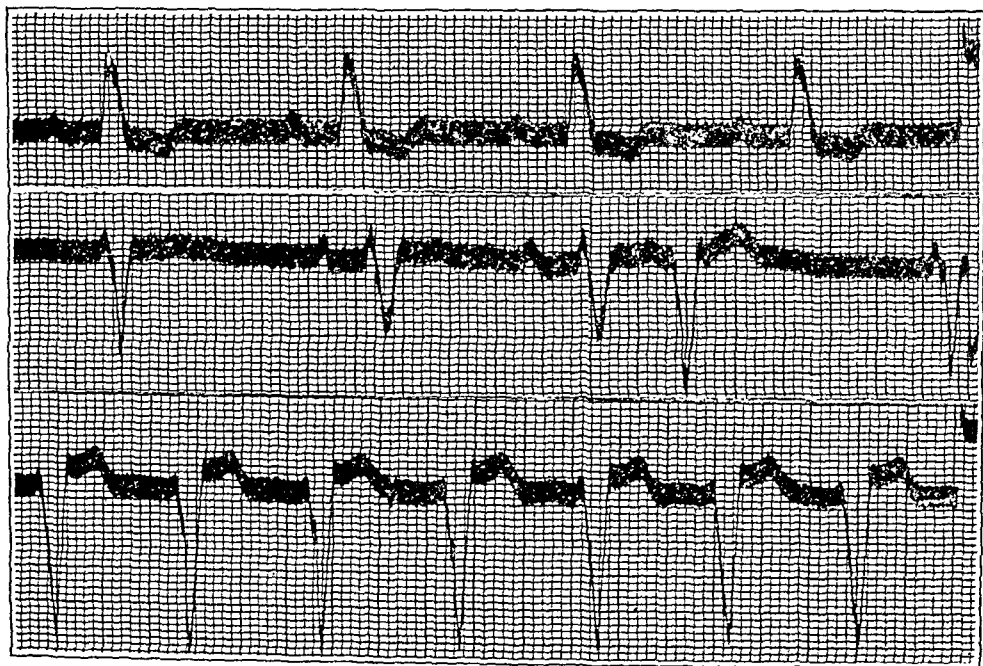


FIG. 4.—Mr. W. W.: Leads I, II and III taken six hours before death, showing right bundle-branch block with numerous extrasystoles. The *P-R* interval was prolonged (0.24), and the third lead showed idioventricular beats at a rate of about 100.

as at entrance. The curve taken six hours before death showed right bundle branch-block with numerous extrasystoles, a prolonged *P-R* interval (0.24), and in the third lead idioventricular beats at a rate of about 100.

The occurrence of these 2 cases in our small series of patients impressed on us the possibility of unfavorable results from too intensive treatment. We were unable to secure necropsy in either case, but the late changes in the electrocardiograms, together with the type of death in both cases, made us feel that the digifolin may have been a contributing factor.

There was extreme decompensation in both cases, and clinical and electrocardiographical evidence showed signs of advanced cardiac degeneration. The factors in these cases which caused death while other patients in like circumstances and under the same treatment improved are impossible to state.

We chose digifolin for use in this investigation because we found it a favorable preparation for use in the three methods of administration. We did not believe that it had any special therapeutic advantages. In most instances a good tincture of digitalis is preferable to other preparations.

The indiscriminate use of digitalis preparations by intravenous or intramuscular methods is not advocated. There are cases in which the severity of the symptoms demands immediate and intensive treatment. It was for these cases that we desired a more accurate and reliable comparison of the three methods of therapy. From our use of digifolin intravenously we do not believe that it carries any greater risk to the patient than strophanthin by the same method.

The relative cost of various preparations is also of importance. In this clinic a good tincture of digitalis is secured for about 15 cents an ounce. An ounce of digifolin costs \$3.90. The average amount of digifolin required to digitalize a patient costs between \$2.50 and \$4.00. Although digifolin costs much more than the tincture, we have not found it to possess any great therapeutic advantage.

Summary. It has been frequently noted that digitalis given intravenously acts more rapidly than when given by mouth. A comparison has been made of different preparations given by different methods.

In comparing the rapidity of action as measured by the slowing of the heart-rate, it was noted that an average slowing of the rate is obtained between three and four hours by intravenous, at about four hours by intramuscular and at six hours by oral administration.

The amount of digifolin required to show the earliest and full therapeutic effects is about equal for intravenous and intramuscular injection. By oral administration it required about half again as much of the drug.

The average time required for digifolin to show the earliest and maximum effects with the three methods of administration has been obtained. The comparison of these time intervals closely approximates the comparison of the digifolin requirements.

The possible unfavorable result of intensive therapy has been mentioned.

The use of digitalis by other than the oral method of administration has not been advocated.

The cost of different preparations of digitalis has been mentioned as an important factor in treatment.

BIBLIOGRAPHY.

1. Withering: *An Account of Foxglove and some of its Medical Uses, with Practical Remarks on Dropsy and Other Diseases*, 1785.
2. Wolfer, P.: *Schweiz. med. Wehnschr.*, 1921, 50, 587.
3. Kottmann: *Corr.-Bl. f. Schweiz. Aerzte*, 1907, 37, 306.
4. Fraenkel and Schwartz: *Arch. exper. Path. u. Pharmacol.*, 1907, 62, 79.
5. Meyer, E.: *Klin. Wehnschr.*, 1923, 1, 57.
6. Hatcher and Weiss: *Proc. Soc. Exper. Biol. and Med.*, 1921, 19, 7.
7. Luthje: *Verhandl. d. deutsch. Kong. f. inn. Med.*, 1913, 30, 159.
8. Wedd: *Bull. Johns Hopkins Hosp.*, 1919, 30, 131.
9. Eggleston and Wyckoff: *Arch. Int. Med.*, 1922, 30, 133.
10. Pardee, H. E.: *Jour. Am. Med. Assn.*, 1920, 75, 1258.
11. Robinson: *AM. JOUR. MED. SCI.*, 1920, 159, 121.
12. Cohn and Levy: *Proc. Soc. Exper. Biol. and Med.*, 1920, 17, 81.
13. Morris: *Minnesota Med.*, 1918, 1, 125.
14. Fulton: *Providence Med. Jour.*, 1914, 15, 28.
15. Pratt, J. H.: *Jour. Am. Med. Assn.*, 1918, 71, 618.
16. Cohn, Frazer and Jamieson: *Jour. Exper. Med.*, 1915, 21, 593.
17. Hatcher and Brody: *Am. Jour. Pharm.*, 1910, 82, 360.

THE EFFECT ON THE BLOOD OF IRRADIATION, ESPECIALLY SHORT WAVE LENGTH ROENTGEN-RAY THERAPY.*

BY GEORGE R. MINOT, M.D.,

AND

ROY G. SPURLING, M.D.,

BOSTON.

(From the Medical Service of the Collis P. Huntington Memorial Hospital of Harvard University.)

Introduction. The physiological effects of exposure to roentgen-rays and radium are assuming increasing importance in clinical medicine; particularly with the advent of the use of apparatus of

* Drs. G. W. Holmes, L. B. Morrison, M. C. Sossman and R. G. Giles administered the treatments. It is a pleasure to acknowledge our indebtedness to them for their helpful suggestions. The coöperation given by the staff is duly appreciated, especially that of the director, Dr. Robert B. Greenough. The careful technical assistance given by Miss Geneva Daland and Miss Margaret Weld is also acknowledged with gratitude. This paper is No. 32 of a series of studies in Metabolism from the Harvard Medical School and allied hospitals. The expense of this investigation has been defrayed, in part, by a grant from the Proctor Fund of the Harvard Medical School for the study of chronic disease.

high voltage delivering short wave lengths. It has long been recognized that desirable therapeutic irradiation produced slight blood alterations, and that excessive irradiation produced profound changes in the hematopoietic system. There has been a general impression that a profound effect on the blood, which might lead to disastrous results, would become prevalent with the administration of the new short wave length therapy. With the installment at the Collis P. Huntington Hospital of Harvard University of a high voltage apparatus designed by Prof. William Duane, a study of the effect of its rays of short wave length on the formed elements of the blood has been undertaken with a view to determining whether a biological reaction occurred that would be of value in indicating the safe use of the apparatus.

Résumé of the Literature. In order to evaluate the known effect of irradiation on the blood, a brief review of the literature is given below. For the benefit of those who wish to study the subject in detail, an essentially complete bibliography is appended. (Articles starred are considered to be the most serviceable.)

The data in the literature on the effects of irradiation on the blood are confusing, owing chiefly to the utilization of many different kinds of apparatus delivering different degrees and qualities of light. Details regarding the amounts of irradiation utilized have often been omitted, hence only generalized statements are made below concerning the blood changes after irradiation with either roentgen-rays or radium.

It has become generally accepted that biological reactions after exposures to roentgen-rays and radium are essentially the same, the degree of reaction depending upon the quantity of irradiation taken into the organism. The location of the exposure appears not to create a fundamental difference in the alterations that occur in the blood. Levin³² states, however, that radium causes less general disturbance to the blood and hemopoietic system than does corresponding doses of roentgen-rays. It is also his belief, from animal experimentation, that the effect of irradiation on the blood is dependent upon the square surface of entry of irradiation into the organism to a far greater extent than upon the size of the dosage administered.

Heineke,^{22a} in 1904, made the first careful histological studies of the blood and blood-forming organs following roentgen-ray exposures. His experiments were made upon small animals. He demonstrated that the lymphoid tissue of the body was primarily affected, and that there developed a degeneration of lymphoid follicles in the spleen and lymph glands, and a diminution in the number of lymphocytes in the circulating blood. He also found that there was a marked diminution in the number of white cells after heavy irradiation, beginning after the second day, with a predomination of polymorphonuclear neutrophils. After several days the lympho-

cytes almost entirely disappeared, while the absolute number of polymorphonuclear and large mononuclear forms showed scarcely any change. From his studies on the bone-marrow he found that the white cells, with few exceptions, were destroyed. This destruction of white bone-marrow cells was apparent in three hours after exposure, and reached its height after eleven hours. The destructive process terminated after five or six days. Heineke noted that the injured bone-marrow was capable of regeneration, which commenced before the destructive action ceased and was completed by the end of the third or fourth week. He suggested that the diminution in the circulating lymphocytes is referable directly to the selective destruction of the lymphogenic tissue by roentgen-rays. These observations on the hemopoietic system have been confirmed by Warthin,⁶⁸ Aubertin and Beaujard,^{4a, 4b} and others.^{30, 38a} It has also been shown^{3, 12, 29, 53, 67} that if the irradiation is sufficient, actual complete aplasia of the marrow occurs with its characteristic peripheral blood picture.

During the next few years, following this pioneer work of Heineke, reports of intensive studies of the circulating blood after irradiation appeared in the literature. Practically all the recorded observations were made on small animals with only an occasional observation on patients. Aubertin and Beaujard^{4b} were apparently the first to report that prior to leukopenia there developed a primary transient leukocytosis. They found that the leukocytosis was due almost entirely to an increase in the polymorphonuclear neutrophils. Since their report many^{4a, 10, 17, 49, 63, 65} have observed that an initial leukocytosis occurs in both animals and man after any amount of irradiation in contrast to the leukopenia which develops only after relatively large doses. The height of this leukocytosis apparently varies in animals and man; in animals an increase of 100 per cent in the number of circulating leukocytes is common, while in man the increase seldom amounts to over 50 per cent. The leukocytosis usually starts about two hours after roentgen-ray treatment, and has reached its height in twelve hours. It persists, on the average, for not longer than twenty-four hours. The height of the leukocytosis does not seem to be dependent upon the character of the irradiation. When radium is used the leukocytosis lasts longer than when roentgen-rays are used; often forty-eight hours. This longer duration may be due to the fact that radium is often applied for a much longer period of time than the roentgen-rays.

All observers^{21, 33, 35, 38, 57, 61, 69, 70} have found that following the leukocytosis there often occurs a marked decrease in the number of white blood cells, especially the lymphocytes. This decrease amounts to an actual leukopenia if sufficient irradiation is used. In experimental animals the white cells have often been recorded as low as 1000 per cu.mm., requiring five to fifteen days before they returned to normal numbers. This degree of reduction of

the white cells rarely has been observed in man following customary therapeutic doses of irradiation, though excessive irradiation may lead to such a reduction. In the early literature, counts of 4000 white cells per cu.mm. are occasionally recorded in man, but such counts were only transient and the normal level was reached in a few days. This contrast between the effects of the rays on animals and man is but one of degree and can be accounted for by the proportional difference in the size of the doses used. However, since the more recent clinical reports of the effect on the blood of large doses of radium and roentgen-rays, leukopenia of greater degree and of longer duration than formerly recorded, is being observed following treatment. Leukopenia, following intensive treatment, has been recorded as persisting from three to five weeks, and Heim²¹ states that it may be even eight to twelve weeks before the white cells return to normal. The advent of the high voltage machine delivering rays of short wave length is not wholly responsible for the recent increase in the frequency of leukopenia. This is because larger doses of irradiation have been employed with all forms of apparatus during the last three to four years. The blood changes now being observed following intensive irradiation are quite comparable to those observed in small animals many years ago, because the large doses now being used therapeutically approach quantitatively the doses originally employed in animal experimentation. It is noteworthy that information in the literature is scant concerning the ease with which leukopenia is produced by second courses of treatment.

To prove whether the leukopenia produced by irradiation is due to a direct effect on the circulating blood or to a suppression of activity of the bone-marrow, Benjamin *et. al.*,⁷ performed some ingenious experiments. They showed that it is possible to produce the characteristic changes in the circulating blood (leukocytosis followed by leukopenia) not only by irradiation of the blood-forming organs, but also by irradiation of the isolated blood. A cardinal difference in the effect of irradiation of the two tissues is that regeneration occurs with astonishing ease in the latter instance, while after the bone-marrow is exposed seven to ten days are required for regeneration. They conclude that the transient changes occurring in the blood during the first twenty-four hours are accompanied by a destruction of leukocytes in the blood stream while the more prolonged alterations are due to injury of the hemopoietic system.

It has been well established that the lymphocytes are the most sensitive of all the blood cells to irradiation. Since Heineke^{22a} demonstrated in animals a diminution of the number of circulating lymphocytes and a destruction of lymphoid tissue following exposure to roentgen-rays, this phenomenon has been investigated by many, 5, 7, 16, 36, 38, 56, 59 especially Mottram^{39, 41} and Murphy.^{44, 45, 47} The

results show clearly that while relatively large doses of irradiation cause a marked decrease in the number of circulating lymphocytes, distinctly small doses act as a stimulus to the lymphogenic organs and cause a lymphocytosis. The degree of lymphopenia is not necessarily proportional to the degree of leukopenia. Quite comparable to the effect of small doses of roentgen-ray or radium irradiation is the effect of the similar light rays from the sun, as it has been shown by Aschenheim,¹ Clark,¹⁴ and others, that there occurs a relative and actual increase in the number of circulating lymphocytes after exposure to direct sunlight.

The percentage of polymorphonuclear neutrophiles varies in inverse proportion to the percentage of lymphocytes at all times following irradiation. The absolute numbers of polymorphonuclears are increased, except with leukopenia, when they may become reduced to 50 per cent of their original number; however, their percentage still remains high.

Coincident with the drop in the lymphocytes, the polymorphonuclear eosinophiles undergo a decrease. None may be observed when leukopenia develops. Later they increase over a period of days to weeks, reaching often above normal and sometimes as high as 15 per cent, then returning to normal in a similar period of time. Aubertin and Beaujard^{4a} found in animals on the fourth day following exposure an increase of eosinophiles that persisted for two to three weeks. Later observations on man by Heim,²¹ Masieri,³⁵ Schroeder,⁶¹ and Koenigsfeld,²⁷ indicate that eosinophilia is a late rather than an early manifestation of the effect of irradiation, the primary rise occurring some weeks after exposure. Petersen and Saelhof^{50a} found eosinophilia (5 to 20 per cent) developed for a number of days following irradiation over the livers of dogs. They did not observe such an increase in eosinophiles after exposures of other organs.

No constant changes in the character or number of polymorphonuclear basophiles have been observed following irradiation.

After irradiation little or no change in the numbers or character of the large mononuclear cells has been discovered by most observers. Wetterer, Band and Nemnick⁷⁰ are the only ones to report that many of these cells appear in the blood stream after irradiation.

Various observers (Aubertin and Beaujard^{4a} and others^{5, 24, 38}) have noted following irradiation of animals two types of histological changes in the white cells of the peripheral blood; one to be interpreted as due to destruction and premature death, and the other indicative of youth. Leukocytes showing evidence of histolysis of the nucleus and cytoplasm with abnormal granulations have been frequently recorded in animals in the first week after exposure. During this period of time fragmented white cells were observed often, and sometimes in abundance. These changes occurred especially in the polymorphonuclear cells, but "mononuclear cells"

(Morris³⁸ includes lymphocytes) also exhibited such alterations. Coincident with the many degenerating cells there appeared in the blood stream an increased number of immature ones. These consisted for the most part of young polymorphonuclear neutrophils although an occasional myelocyte was observed. The occurrence of degenerating and immature cells in man after irradiation has been referred to but little.

There are relatively few observations recorded on the effect of irradiation on the blood platelets. Helber and Linser²⁴ and Duke¹⁹ found that there was a decided decrease in the number of circulating blood platelets in small animals following heavy irradiation, while smaller doses apparently stimulated their production and caused a rise. Similar observations of the effect of radium are recorded by Mottram.^{39c} Bucky and Guggenheimer^{9a} among others have observed over 100 per cent increase in the number of blood platelets in man following erythema doses of roentgen-rays.

✓ The effect of irradiation on the red cells and hemoglobin is not so clearly defined in the literature as the effect on the white blood cells. It is evident that important changes do not occur after customary therapeutic irradiation unless repeated many times. Some have reported that if considerable anemia exists then the red cells are adversely affected. ✓ Heineke,^{22a} in his earliest observations, found no change in the number or form of the red cells or the amount of hemoglobin during the first twelve days after exposure to the roentgen-rays. During the third week he found that there was a slight decrease in both of these elements. His later observations in the clinic failed to support this view, however, as he found a decided increase in the red cells and hemoglobin in patients after roentgenotherapy. It is evident from reports that fluctuations in the hemoglobin and red cells occur after irradiation, but confusion arises owing to a lack of a distinction between the effects of irradiation and changes in the blood due to improvement of the patient. The current opinion seems to be fairly evenly divided between those ^{8, 9a, b, 15, 21, 22a, b, 61} who believe that there is an increase and those ^{3, 10, 20, 25, 39b, 55, 62} who recognize a decrease in the number of red cells and the percentage of hemoglobin, and those ^{6, 36, 38, 60} who believe there is no appreciable change in these two elements after irradiation. It seems probable that this difference of opinion may be due to variation in the size of the dose of irradiation used, as well as variations in the health of different patients. It is well known that prolonged and excessive exposure to irradiation may lead to anemia^{29, 53} an ill-effect that never has been observed after a single exposure. Nucleated red corpuscles have been noted in the circulating blood of animals, but not in man when the bone marrow was essentially normal, following large doses of irradiation. No distinct or constant alterations in the size, shape, or staining qualities of the red blood corpuscles

have been observed in man or animals following therapeutic irradiation.

The blood picture of those people chronically exposed to irradiation, as roentgen-ray and radium workers, is extremely variable and does not directly concern us here. Suffice it to say, that the blood picture may be one that indicates varying degrees of marrow insufficiency, while occasionally, if the exposure is sufficient, actual aplasia may develop.

Cases Studied and Methods. From the above résumé of the literature, it is evident that there is ample information indicating that sufficient irradiation of any part of the body leads to lymphopenia and leukopenia. In spite of the lack of comprehensive data in the literature, it would appear that the degree and duration of the lymphopenia and leukopenia are more marked and longer with a larger than a smaller dose; that though the degree may be the same with different doses, the duration will be longer with the larger dose. The effect of the amount of surface area irradiated has been shown to play an important part in alteration of the blood in animals, but in man little attention has been given to this factor. Investigations reported below were undertaken with a view to determine the degree and duration of changes in the white cell count produced by desirable therapeutic doses of short wave length roentgen-rays as contrasted with roentgen-rays of longer wave length in patients not suffering from any fundamental disorder of the hemopoietic system. In addition to the white cell count, observations on all the formed elements of the blood were made to determine what changes occurred and to learn how further to evaluate alterations of the blood in regard to safe and efficient treatment.

The data presented were obtained on 42 patients with various forms of malignant disease.* These cases have been divided into three groups dependent upon the amount of irradiation given. The first two groups consists of 20 cases, each of these patients was studied before and after one course of treatment received from one of two different roentgen-ray machines, delivering many long and some short wave lengths. Both of these machines represent types of apparatus which are commonly in use for therapeutic purposes at the present time. Of these 20 patients, 8 were given from one machine† and 4 from another‡ a smaller dose of roentgen-

* The clinical diagnoses were as follows: Carcinoma of breast, 18; of esophagus 3; of sigmoid, 3; of pancreas, 2; of prostate, 3; of testicle, parotid, tongue, palate, uterus, 1 each; hypernephroma, 2; mediastinal sarcoma, 2; 1 each of melanotic sarcoma, malignant tumor of chest wall (undiagnosed), sarcoma of fascia of thigh, retroperitoneal sarcoma.

In selecting this group of cases an attempt was made to exclude those in whom the hemopoietic system was obviously involved by malignant disease. Of course this does not mean that patients showing secondary blood changes associated with advanced malignant disease were excluded.

† Operated at 90,000 volts, a 9-inch spark-gap, and with the target placed 12 inches from the body of the patient.

‡ Operated at 80,000 volts, a spark-gap of 8 inches, and with the target placed 16 inches from the body of the patient.

ray than that received from the latter apparatus by the 8 remaining individuals. The maximum dose given to any of the 12 former patients, who compose the first group, was 424 m.a.m., while the minimum dose was 144 m.a.m.; 3 mm. of aluminum and one sole leather filter was used. The treatment was given in two parts with an interval of four days between each part. The surface area of body exposed (portal of entry) was on an average 434 sq. cm.

The character of the larger treatments given the 8 patients who comprise the second group was as follows: The total dose varied between 630 and 1050 m.a.m.; 4 mm. of aluminum and one thickness of sole leather was used as a filter. The total treatment in each case was divided into four or five parts. In 6 of the 8 patients the total treatment was completed in the course of one week. In the other two, however, the total treatment was prolonged over two and a half weeks. The square body surface irradiated averaged 525 sq. cm.

The 22 patients composing the third group were studied before and after receiving 36 separate courses of roentgen-ray treatment from a new form of apparatus delivering great quantities of very short wave length roentgen-rays. This machine was operated at an equivalent voltage of 220,000 and the target placed 31 inches from the body of the patient; $\frac{1}{2}$ mm. of copper was used as a filter. The total dose of any one course of treatment varied from 338 m.a.m. to 1950 m.a.m. Twenty-five of the treatments were given to 15 of these patients; each one of which was completed within a period of twenty-four hours and usually in less than seven hours. The remaining 7 patients received 11 treatments which were divided into four parts and given on four successive days. The surface area of the body irradiated averaged 940 sq. cm. for the 36 treatments.

The following blood examinations were carried out on each of the 42 patients comprising the three groups. Prior to irradiation, one and sometimes more determinations were made of the total and differential white cell count, red cell count, hemoglobin percentage and platelet count or estimation of the numbers of platelets. The detailed character of the formed elements was recorded. With the exceptions noted below these observations were repeated each day for six days following the conclusion of treatment.* The exceptions were that red cell and platelet enumerations were made daily on but 13 patients, and every few days on the others. After six days the patients were discharged from the hospital, and then the different blood examinations were repeated in most cases at least once each week, or four to five weeks or until the blood findings were similar to those observed prior to irradiation.

* "After-treatment," as used throughout this paper, means after the completion of treatment when it is given at one sitting. On the other hand, when the treatment is divided into four parts, the time "after-treatment" is taken from the completion of the second part.

The Blood of the First Group of Patients. The 12 patients of the first group who received the smallest dosage of all showed about a 20 per cent rise in the white count within the twenty-four hours following treatment. A further rise of 50 per cent during the next seventy-two hours was common. In no case was there a substantial decrease in the number of white blood cells during the period of observation. In some instances the white blood cells returned to their pretreatment level in seventy-two hours, while in others they remained above the pretreatment level for about ten days. The differential count showed no noteworthy changes except for a moderate reduction (20 to 25 per cent) in the number of lymphocytes during the first twenty-four hours. In one case the number of lymphocytes increased for one day. Following treatment the red blood corpuscles and hemoglobin showed no definite changes, but the platelets showed as a rule a slight rise. Degenerate changes of the white cells were frequently noted, especially in the polymorphonuclear leukocytes during the first five days following treatment. These fragmented white cells occasionally rose to as high as 15 per 100 formed white cells.

The Blood of the Second Group of Patients. The 8 patients of the second group who received more intensive treatment than those of the first group showed distinctly greater fluctuations in the white cell count than those receiving smaller doses. All of the 8 patients showed at least a 20 per cent increase, the maximum being 100 per cent, at the end of twenty-four hours following treatment. Following this rise, 2 cases showed no substantial decrease in the leukocytes, the count remaining elevated, in the neighborhood of 12,000 per cu.mm., as prior to treatment. After the transient rise, the white count of the other 6 cases then fell, reaching in three days a point below the pretreatment level. In 4 cases, leukopenia occurred, the white cells averaging 4500 per cu.mm., the lowest count recorded being 2600 cells per cu.mm. The leukopenia usually occurred on the third or fourth day following treatment, but in 1 case it developed as late as the ninth day. The duration of the leukopenia was from one to eighteen days, with an average length of about one week. The patients to develop leukopenia were those in whom the interval between treatments was shortest, and also in whom the total body surface exposed was greatest. When leukopenia did not occur, the pretreatment level of the white count was reached in one to two weeks, and when it did occur, it took about three weeks before the count returned to this level.

The differential white cell counts after irradiation in each of these 8 patients showed a distinct decrease of the circulating lymphocytes, often amounting to as much as a 50 per cent decrease. These cells began to drop immediately after the first part of the treatment, and remained decreased for a period of from two to three weeks, no matter whether leukopenia occurred or not. The poly-

morphonuclear neutrophiles were correspondingly increased in percentage. The other white blood cells showed no definite change in numbers. The blood platelets became definitely increased (33-100 per cent) during the first three days following treatment, and then returned to the vicinity of their pretreatment level. Changes in the character of the white cells were noticed, as in the cases of the first group who received smaller doses of irradiation. Degenerated white cells, to even as many as 20 per 100 perfect ones, were observed in the blood during the first week after treatment. The red cells and hemoglobin showed slightly irregular fluctuations but no constant changes.

The Blood of the Third Group of Patients Treated by Intensive Short Wave Length Roentgen-ray Therapy. The most particular information we have sought has been the effect of heavy irradiation—intensive short wave length therapy—on the formed elements of the blood, particularly the leukocytes. It was the third group of 22 patients that received 36 separate courses of such irradiation. The blood changes in these individuals were similar to, but decidedly more marked, than those observed in the second group. Greater blood changes carry more clinical significance than lesser ones, and those that occurred in this third group of patients are described and discussed below.

The White Count. During the first twenty-four hours following the intensive treatment of these patients there was a rise in the white count. This leukocytosis was transient and had usually run its course by the end of the first day when the white cells were 600 to 9000, usually 2000 per cu.mm.; more than before irradiation. Then there occurred a sharp fall in the white count, so that usually on the second day it was below the pretreatment level. In all instances the count fell further, but more slowly, reaching on the average the lowest point on the sixth day following treatment. At this time, actual leukopenia (less than 5000 cells per cu.mm.) was present in 14 patients (63.6 per cent). Leukopenia occurred as soon as the second day in 2 cases, but the lowest level of the white cells was not reached until the fifth day. The white count of 1 case was at its lowest point as late as the twelfth day after treatment. This patient had a white count of 11,300 per cu.mm. before treatment and never showed an actual leukopenia. In 1 case the white count dropped to 2600 cells per cu.mm., and in 3 others was as low as 3200 cells per cu.mm. The duration of leukopenia was from two to thirty-one days, with an average of about nine days. Leukopenia occurred over fourteen days in 8 instances. However, the white count of at least 50 per cent of the cases did not return to the pretreatment level for four to five weeks.

In order to facilitate the study of the white cells after the 36 different courses of treatment given this third group of patients, the observations were divided arbitrarily into two groups: those

showing leukopenia (below 5000 white cells per cu.mm.), and those not showing leukopenia. The mean total white count and absolute number of the different white cells of the two groups are shown in Figs. 1 and 2. The first group comprises data obtained before and

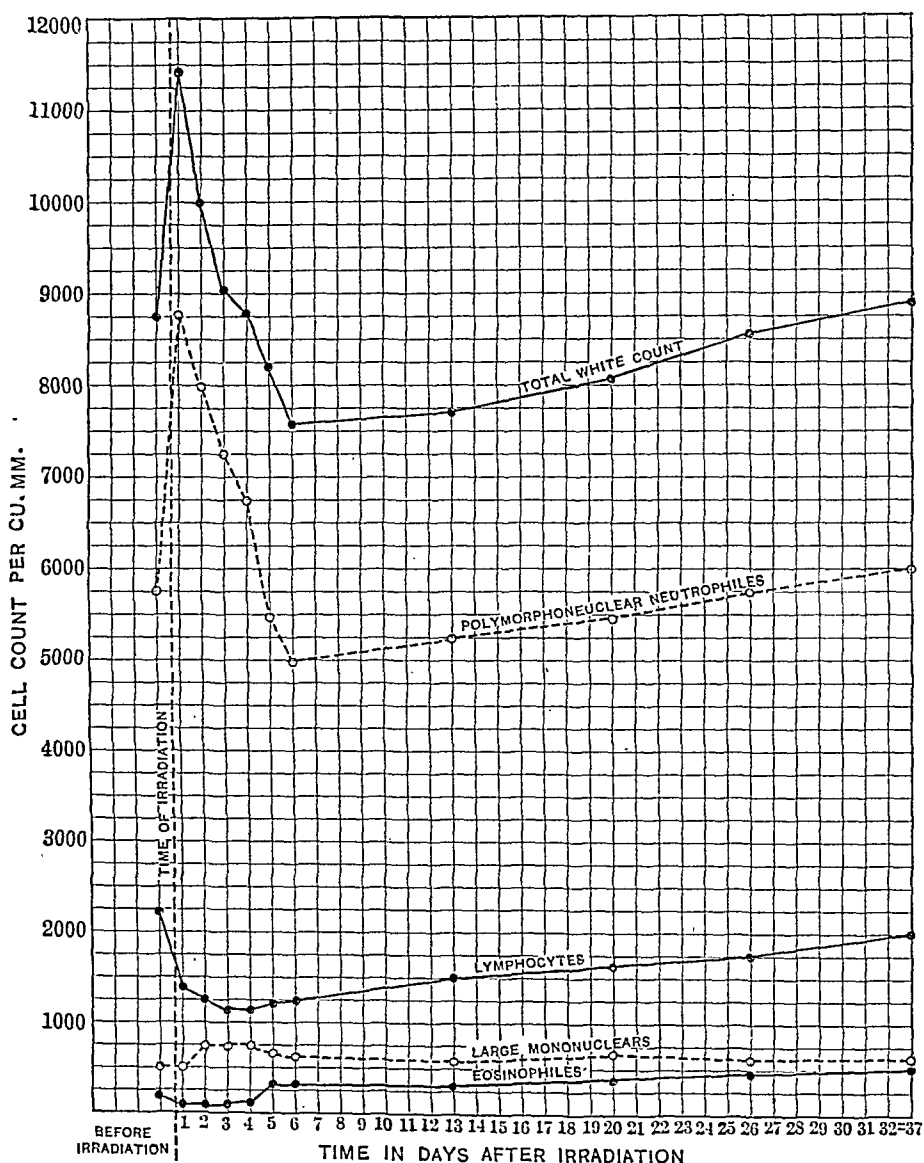


FIG. 1.—The mean total white count and absolute number of the different white cells per cu.mm. before and after twelve short-wave-length roentgen-ray treatments given 8 patients with malignant disease, who did not develop leukopenia.

after 24 courses of treatment given 14 patients, while the second consists of the observations before and after 12 courses of treatment administered 8 patients. The two figures show that in both groups the general trend of the curves for the total counts is the same, the variation being in the degree rather than in the character. Fluctu-

ations in the curves occurred in individual cases when the cause was obviously due to the primary disease or complications of the disease rather than the effects of irradiation *per se*. The pre-treatment counts of those patients showing leukopenia were lower than those

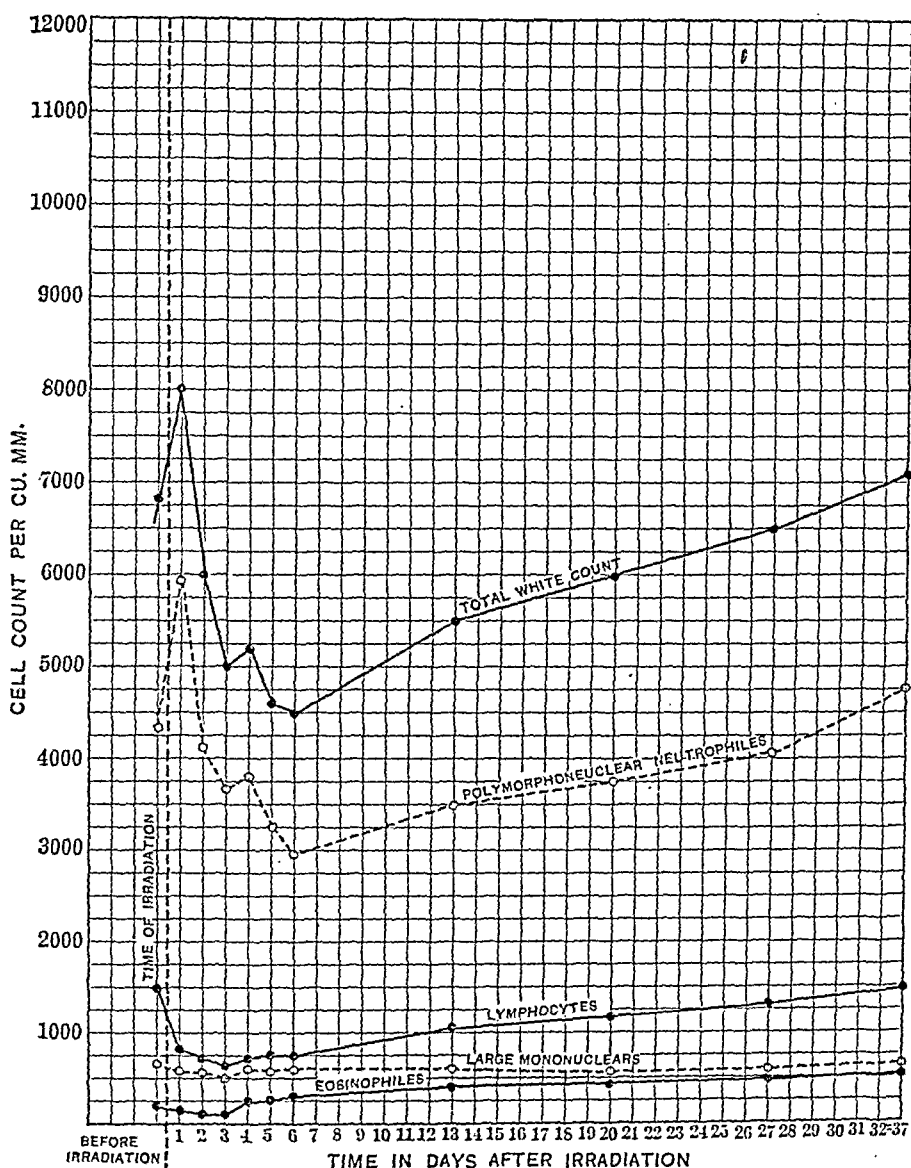


FIG. 2.—The mean total white count and absolute number of the different white cells per cu. mm. before and after twenty-four short-wave-length roentgen-ray treatments given 14 patients with malignant disease, who developed leukopenia.

in whom leukopenia was not produced. The height of the pre-treatment count may well be a factor in determining whether leukopenia will be produced or not. Even so, there are other and undoubtedly more important factors leading to the production of leukopenia that are to be considered later.

The data show that the effect of more than one treatment on the white cells depends not only upon the length of time elapsing between each course of treatment, but also upon the condition of the hemopoietic organs as reflected by the number of white cells present in the peripheral blood. If the white count has had sufficient time to return to its normal level, treatment of the same character as given before then produced changes similar to those occurring following the first treatment. If, however, second or third treatments were given before the cells returned to their original levels, leukopenia of greater degree and duration was produced. If a second or third treatment was given when the white count had just returned to normal, it appears from somewhat meagre data that leukopenia became more pronounced than if the normal white cell level had been established for some time. To 4 of the patients a second, and in one instance, a third, treatment was administered when leukopenia existed. In these instances the degree and duration of leukopenia was more marked than in any of the other cases; the lowest count recorded (2600 per cu.mm.) and the most persistent leukopenia (thirty-one days after the last treatment) occurred under these circumstances. No untoward clinical symptoms developed, however, following treatment given during leukopenia. Four cases (not included in the 22 of Group III) observed recently have received a second as well as a third treatment while leukopenia was present that developed following the first irradiation. All four have improved, and the white count is above 5000 per cu.mm. eight weeks after the last treatment.

The Lymphocytes. As Figs. 1 and 2 show, there was a prompt decrease in the number of circulating lymphocytes in practically every case of this third group. The fall was greatest during the first twenty-four hours, but continued for three days in nearly all the cases coincident with the decreasing white count. The lymphocytes usually remained at a low level for the next three days, and then rose very slowly for three to four weeks, rising proportionately more slowly than the white count. In three to four weeks they usually reappeared in normal numbers although at this time they were often below their pretreatment level. There were three instances when the lymphocytes did not decrease after treatment. However, in these instances the pretreatment level was low, evidently because a course of treatment had been given before. Occasionally the lymphocytes dropped from either a high or low normal percentage to a level of from 1 to 3 per cent, usually over a period of five days, but in 1 case within forty-eight hours. The degree of lymphopenia in this group of patients was distinctly more marked than usually observed in the other two groups who received less treatment and had less body surface exposed. A second or third treatment affected the lymphocytes in a similar fashion as the total white count. In some such instances when the

lymphocytes did not drop further, the persistence of their low level was of longer duration than usually seen after a first course of treatment. Likewise, as a rule, second treatments usually caused a longer duration of lymphopenia than leukopenia, and kept the lymphocytes low in proportion to the white count longer (sometimes weeks) than occurred following the first irradiation, so that lymphopenia is the last blood change to be readjusted. This only further indicates that the lymphocyte is the most sensitive cell to the rays.

The Bone-marrow White Cells. The curve of the polymorphonuclear neutrophiles follows that of the total white count very closely. The increase in the number of these cells seems to be responsible for the initial leukocytosis as the actual numbers of all the other cellular elements of the blood were either stationary or markedly decreased. During the period of leukopenia, the absolute numbers of polymorphonuclears were decreased, rarely as much as 50 per cent, though their percentage number was increased above normal.

Prior to irradiation in this third group of patients, the polymorphonuclear eosinophiles were never above 4 per cent. Following treatment, these cells decreased, as did other blood elements, for three or four days. However, these cells were seldom if ever absent from the blood even during the period of leukopenia. Following this primary decrease there occurred a relative and absolute increase of eosinophiles, usually starting at about the end of the first week and reaching a maximum during the second or third week after irradiation. Four of the patients showed respectively 9, 10, 12 and 23 per cent of eosinophiles, and 5 others had 5 per cent or over at some time during the second and third week following treatment. All but 3 patients showed 3 to 4 per cent of eosinophiles during this time, which was a greater number than was found in the first week after irradiation. The highest percentage of eosinophiles appeared in those patients who had received several treatments with the high voltage machine. One patient, who has received four separate courses of the short-wave-length treatment over the chest in the past fourteen months, has shown a slow but progressive increase in the number of eosinophiles, from 2 to 23 per cent.

Eosinophilia following irradiation appears to occur particularly as a result of repeated exposures, as shown by our observations and those recorded in the literature. This increase of eosinophilic cells does not seem to be related to the diseased state of the patient. An increase of these cells has been reported by others as occurring in those persons chronically exposed to radium and roentgen-ray, and we have commonly observed slight eosinophilia in such individuals. This information serves to further indicate that the eosinophilia observed after persistent therapeutic irradiation is not necessarily due to disease.

The number and character of the polymorphonuclear basophiles showed no constant variation from the normal.

The absolute numbers of endothelial leukocytes (large mononuclear and transitional cells) were not changed to any appreciable extent after irradiation. Coincident with the rising white count they tended to be slightly increased (10 per cent). In 2 cases these cells were 12 per cent before treatment and continued elevated afterward, when there was a relative and actual increase of their numbers during the second and third week.

The Occurrence of Degenerated White Cells. The destructive or inhibitory action of irradiation on lymphatic tissue is reflected in the peripheral blood by lymphopenia, while its similar effect on the marrow is shown particularly by a decrease of the white cells derived from it. We have observed that large numbers of broken and degenerated white cells appear in the blood stream of man after irradiation, which further indicates the destructive action of the rays. The occurrence of such cells has been noted in animals, but scant reference has been made to their presence in man. Great numbers of such cells in many fantastic fragments and forms, together with increased ameboid activity of formed cells, are common following irradiation in cases of leukemia, but we have reference here to the presence of degenerated white cells in individuals not suffering from primary blood disorders. Such cells formed a distinct feature of the blood in all the 36 patients of the three groups but particularly in the 22 patients treated intensively with short-wave-length therapy.

The destruction does not seem to be limited to any one variety of cell. Many, however, were so degenerated that proper classification was impossible. The greatest number of these cells appear during the first three days after treatment and slowly diminish in number during the next three days, but do not reach a normal level until the second or third week following irradiation. They occurred most profusely when leukopenia and lymphopenia were marked, although they were repeatedly observed in patients with slight changes in the numbers of white cells. It was common to find in the third group of patients 25 to 30 of these cells per 100 formed white cells during the first three days following irradiation. In one there were 50 degenerated cells per 100 formed white cells observed within the twenty-four hours following treatment. Thus the numbers of such cells observed after the larger doses of irradiation given the third group of patients were greater on the average than the numbers seen after the smaller doses given the patients of Groups I and II.

The Presence of Immature White Cells. Besides the histological features of the white cells indicative of premature death, a second form of histological change, little commented on in the literature, was observed in these cells after irradiation. This consists of signs indicative of youth. Youthful polymorphonuclear cells (uni- and bilobed neutrophile polymorphonuclears with often rather coarse granules) from the marrow began to appear in abnormal numbers

about four days after irradiation, particularly in patients of the third group, but also in those of Group II. No greater numbers were observed whether leukopenia was present or not. The occurrence of these immature forms persisted approximately until the white count returned to its pretreatment level. It was common to observe from 3 to 5 per cent of such cells, and 10 per cent represents the maximum number. The greatest number occurred shortly following the time that the white count was at its lowest point. Immature forms of large mononuclears were also observed during the period of leukopenia. The presence of distinct increases of immature lymphocytes was not observed. Occasionally a few atypical mononuclear cells appeared that may well have been immature forms of lymphocytes. No myelocytes were observed. The occurrence of these youthful cells simply indicates that following the inhibitive action of irradiation, normal, orderly regeneration occurs. Their absence, however, should not necessarily be taken to indicate an unfavorable feature.

The Blood Platelets. Immediately after the intensive treatment given this third group of patients, the blood platelets often showed a transient increase in their numbers. Then a slight decrease for a few days occurred; by count, seldom more than 75,000 per cu.mm. In 1 patient, the platelets decreased to the vicinity of 100,000 per cu.mm. when the white count was about 3000 per cu.mm. These elements derived from the megacaryocytes of the marrow appeared to be depressed less readily than the leukocytes, though following repeated exposure their number may become so few that a state of chronic purpura hemorrhagica exists, as observed in some roentgen-ray workers. In this third group of patients, about the fourth day after irradiation, usually some days prior to a definite rise in the white count, the platelets increased so that in a few more days they were commonly found in greater numbers than normal. Increased numbers were then observed for a few days to a few weeks. The increase though definite (usually 125,000 per cu.mm. above normal) was seldom marked. More marked changes in their numbers and character do, however, occur following heavy irradiation in some cases of disease of the hemopoietic tissue. No noteworthy changes in the character of the platelets were observed in any of the 36 patients.

The Red Blood Corpuscles and Hemoglobin. No characteristic or constant changes in the number of red blood corpuscles and hemoglobin percentage were observed in these patients irradiated intensively, the same being true for those of Groups I and II. There is no question that fluctuations in the number of red blood cells and hemoglobin occur as the result of irradiation as shown by numerous reports, particularly the more recent ones, as well as by the observations we have made. However, neither increases nor decreases occurred with any constancy in our patients. We can

record in the first few days after treatment both increases and decreases of 500,000 red cells per cu.mm., while no cases showed as great a variation as 1,100,000 per cu.mm. during this period of time. It would seem that the therapeutic doses given, tended more often than not, to permit a transient slight decrease in the red blood cells for a few days after treatment. As noted above, excessive irradiation can lead to distinct anemia, but even many repeated intensive doses given at intervals of more than six weeks have not led to anemia. In fact, 2 cases in our series that received four courses of treatment showed not a decrease but a progressive marked increase in the red count. This is to be attributed to the effect of irradiation in decreasing the activity of the condition that was responsible for the anemia. Those patients that were distinctly anemic* before treatment did not have any greater changes in their red cell count or white cells soon after irradiation than those without anemia. No definite histological changes in the erythrocytes were observed which could be attributed to irradiation. Fluctuations in the numbers of immature red cells, that tend to parallel the numbers of white cells, do occur and will be reported upon by Dr. Isaacs of this clinic.

Consideration of the Cause of the Degree of Leukopenia and Lymphopenia. It is evident from the observations recorded above, as well as those in the literature, that the new short-wave-length roentgen-ray therapy, when properly used, produces no changes in the blood that are of a different character than those occurring after milder yet intensive therapy from other forms of apparatus or radium; nor changes that are serious for the patient, provided they are not ignored. It is clear that the most important blood changes are leukopenia and lymphopenia. The changes in the white cells that occur following irradiation tend in general to vary in direct proportion with the size and intensity of the dose, so that large doses of short rays are more effective in producing leukopenia and lymphopenia, than large doses of long rays, and greater rather than smaller doses of either cause a more distinct effect on the white cells.

The portion of the body irradiated does not appear to importantly influence the degree of alteration in the white cells. It has been our impression that irradiation of the abdomen might lead more often to a rapid and longer lasting leukopenia and lymphopenia than irradiation elsewhere. However, our data and those in the literature do not clearly indicate such to be the case. Petersen and Saelhof's studies do suggest that if the abdomen is exposed greater blood changes occur than when irradiation is applied elsewhere.

In our cases, however, the degree and the duration of the changes in the white cells have varied within wide limits when the amount

* In this series 1 with 50 per cent and 4 with about 60 ger per cent hemoglobin. In addition 4 cases recently observed with 25 to 50 per cent hemoglobin.

of treatment as measured by purely physical standards indicating size and intensity of dose has been the same. Some of the patients receiving the largest doses did not have leukopenia, while some of the instances of profound leukopenia occurred following doses half the size of the maximum dose.

Recognition must be given to the fact that the influence of any substance on the blood will be modified by the state of the individual's hemopoietic organs, which owing to disease and its complications will vary in different patients. It was recorded above that the initial height of the total number of white cells and lymphocytes might play a role in determining the degree and duration of their decrease following irradiation. Our data show no further distinct correlation between the clinical condition of the patient with malignant disease: including the amount of anemia present, (even with hemoglobin 50 per cent) and the amount of alteration observed in the white blood corpuscles after irradiation.

It is clearly evident that the size and intensity of ray dosage is a much more important factor in the production of leukopenia and lymphopenia than any state of the patient. There is, however, another factor of importance as shown by Levin's³² work on animals, but which heretofore has been neglected in the clinic. This factor is the amount of surface area irradiated. An analysis of our data shows that the intensity and duration of the leukopenia and lymphopenia is on the average in direct proportion to the square surface of the body exposed to the rays, that is, their portal of entry. Thus one would expect that a large dose applied over a large area would produce a more profound effect on the formed blood elements than a similar large dose applied over a small area, and such is borne out by our observations. In both instances the leukopenia and lymphopenia may become of the same degree, though usually more marked with the greater portal of entry of the rays. However, the duration of the white cell changes will always last longer when the radiation is over a larger rather than a smaller area. Table I summarizes the data concerning the effect of dosage* and the portal of entry of the rays on the white cells.

The amount of secondary radiation produced in a patient is proportional to the three chief factors: The size of the dose, the wave lengths administered, and the size of the portal of entry, factors that determine the amount of reaction the white cells will show, exclusive of inherent differences in patients themselves. In some cases this secondary radiation amounts to as much as 40 per cent increase in the size of the dose administered by the short wave length machine used to treat the patients of the third group. This

* The dose measured in electrostatic unit seconds is approximately comparable to that measured in milliamperè minutes. Data for the former are not available for this whole series of cases. About one thousand electrostatic unit seconds were given those patients more recently treated with the short wave length apparatus/

phenomenon indicates how the actual dosage becomes bigger not only with shorter than longer wave lengths but also with a larger portal of entry. One might consider that this additional radiation accounted for the greater degree of leukopenia and lymphopenia observed when a greater rather than a smaller area was exposed. This secondary radiation is probably an important factor, even so the direct exposure of a greater amount of blood and tissue as occurs with a larger portal of entry probably plays a role in the production of the blood changes.

THE RELATIONSHIP BETWEEN THE ROENTGEN-RAY DOSE, THE SURFACE AREA OF THE BODY EXPOSED, AND THE ALTERATIONS IN THE WHITE BLOOD CORPUSCLES.

Group.	Number of courses of treatment.	Roentgen-rays.	Average dose in milliamperè minutes.	Average sq. cm. of body surface exposed.	Alterations in white cells.
I . .	12	Chiefly long	250	434	Very slight.
II {	A. 4	Many long and some short {	800	331	Slight; no leukopenia.
	B. 4		945	678	Typical; brief duration; leukopenia.
III {	A. 12	Many short {	1090	665	Typical; moderate duration; no leukopenia.
	B. 24		1020	1050	Typical; long duration; leukopenia.

The Clinical Significance of the Blood Changes. The biological reaction of the white cells produced by irradiation has clinical significance. It may perhaps give information regarding the future state of the patient, and does aid to determine the dose of irradiation, particularly for individuals previously treated. Claims have been made by Westman,⁶⁹ Maseiri,³⁵ and Heim,²¹ for example, that cases favorably affected by the rays show less pronounced blood changes after irradiation with more rapid restoration, especially of the lymphocytes, than refractory cases. We have not at hand sufficient data to prove or disprove this assertion. However, among our cases are some who had marked and prolonged leukopenia and lymphopenia, and who appeared to be definitely benefited by treatment, more so than some others who did not present such profound changes in the blood. Whether greater benefit would have occurred if irradiation had been given without producing as marked blood changes is problematical.

It is possible that this biological reaction of the hemopoietic tissue might serve as a measure for determining the most suitable dose of irradiation, because like doses measured by physical methods

produce different effects, not only on similar tumors in different patients, but also different degrees of depression of hemopoietic tissue. A study of many cases will be necessary in order to predict the exact influence on the blood of a given dose in a given case. It would be interesting to study the degree and character of improvement of a large series of cases to whom intensive treatment was given without producing leukopenia and but transient lymphopenia as contrasted with a similar series of cases where treatment permitted distinct blood changes for some time. The patients whose white cell counts are averaged in Figs. 1 and 2 perhaps give such a comparison. But the data are too meagre to draw from them conclusions of this type. There is at least a suggestion that those cases not showing leukopenia did better than those that did. Others, as noted above, have reported the same.

Neither our data nor those of the majority of others show that there is any relationship between the amount of "roentgen-ray sickness" and alterations in the formed blood elements.

Depressed activity of the marrow as shown in the peripheral blood by leukopenia with a decrease of the bone-marrow white cells as well as decrease of the platelets and immature red cells must be looked upon as an undesirable state. Likewise lymphopenia indicative of decreased lymphoid activity is an undesirable condition in many instances. It has been pointed out that increases of lymphocytes may favor immunity to cancer,^{46, 47, 48} so that on this account alone a decrease of these elements is not ideal. Even so, leukopenia and lymphopenia may occur without there being any obvious detrimental effect, and in the effort to treat the patient most adequately the production of such blood changes may be an unavoidable circumstance. They are also of much less importance than the amount of benefit obtained from doses causing depression of hemopoietic tissue. One cannot believe, however, that it is wise to produce marrow and lymphoid depression for a considerable period of time. In so doing, a tumor may be markedly decreased, but to obtain such a result the hemopoietic system might be so severely injured as to function very inadequately. Ideally one would like to be able to obtain the effect upon malignant disease given by intensive irradiation without producing depression of hemopoietic tissue. At present this does not appear easy to accomplish, and our data, as well as those of others, show that the relatively transient depression of the hemopoietic tissues is not alarming. In fact, treatment may be given in the face of leukopenia without necessarily any disturbing circumstances arising. One must bear in mind, however, that repeated doses may cause an increasingly greater degree and duration of depression of the marrow. The effect is quite comparable to other marrow reactions; for example, that observed after recurring blood loss.¹⁸ Following one hemorrhage many young red cells appear in the blood stream and

the red count soon returns to normal, while following an equal amount of blood loss after repeated hemorrhages the young forms increase less and the numbers of red cells return more slowly to normal.

It is certainly very desirable to examine the blood before any irradiation treatment, particularly when intensive irradiation has been given before. A white count alone will usually suffice for practical purposes. If the count is found normal or elevated, there is no question but that treatment may be given without any fear of doing harm to the hemopoietic tissues. If this count has only just returned to normal following depression from previous treatment, a greater or more lasting depression will occur than if the cells had been established at a more normal level for some time. This should be recognized if one desires to give treatment without creating depression of the hemopoietic tissues. Also the effect of disease itself on the blood picture is to be taken into account when one is evaluating analyses. Though treatment may be given in the face of leukopenia without any inherent danger, it is probably wiser not to do so; becoming a more serious event each time treatment is repeated in the same case under such circumstances. Thus, in deciding whether or not to treat a patient with leukopenia, one must attempt to decide if the disease has reached such a state that treatment of it is desirable, in spite of the creation of an increased depression of the hemopoietic tissue. This latter condition may become of relatively little importance and be distinctly less harmful than permitting the lesion to go untreated. Before it is finally decided to give treatment when leukopenia is present, further blood examination should be made, because this may reveal a more serious depression of the marrow than a white count alone. For example, if under such circumstances the blood platelets are found to be distinctly reduced it would indicate a much more profound depression than if they were not; then treatment might possibly cause a serious effect.

It is conceivable that it is of greater importance to consider the absolute number of lymphocytes present before irradiation of cancer than the total white cell count. To do so requires additional time and it does not seem essential to obtain this information, though when treatment of diseases of the lymphatic tissue is being considered, a careful histological study of the blood should supplement the white count. In comprehending the effect of therapy one must bear in mind how it acts on lymphocytes, because if one could permit them to remain elevated and at the same time favorably effect the lesion to be treated, it probably would be beneficial.

Some have considered that the development of an eosinophilia is a favorable finding for prognosis. Such may be the case in spite of the fact that it seems to be a result particularly of repeated exposures.

There appears to be no further particular clinical significance to be attached to other alterations in the formed elements of the blood than those discussed above, including the fact that no important relationship has been found between the patient's future clinical state and the number of degenerated white cells appearing in the peripheral blood after irradiation.

So that confusion shall not arise, it is pointed out here that the cases reported upon in this paper and the discussion given does not refer to patients with fundamental disease of the bone-marrow or lymphatic tissue. The evaluation of blood examinations must be taken differently when considering irradiation in many such patients.

Summary. 1. The literature concerning the effect of irradiation on the formed elements of the blood is confusing. A review and essentially complete bibliography is given.

2. A study has been made of the blood of 42 cases, chiefly of cancer, before and after 56 roentgen-ray irradiation treatments. Particular attention was given to the observations on 22 of the patients given 36 intensive short wave length treatments. The other irradiations were milder. Cases of disease of the hemopoietic tissue are not included and the statements below require modification when applied to such conditions.

3. The most important effect of customary therapeutic doses of irradiation on the blood elements is to decrease the number of white cells, especially lymphocytes, so that leukopenia and lymphopenia may occur. Preceding the decrease in the white count a transient increase develops, due to increment of polymorphonuclear neutrophils. Very small doses of irradiation may permit a lymphocytosis.

4. When a customary therapeutic dose of short wave length roentgen-rays is given, it causes the white count to reach its lowest point about six days later; at that time leukopenia (a count below 5000 per cu.mm.) is more often present than not. A decrease below normal of the absolute numbers of bone-marrow white cells, which is indicative of marrow depression, is not unusual. Leukopenia lasts on the average about nine days, but may persist for over four weeks. Even if the white count remains above 5000 per cu.mm., the white count often does not return to its pretreatment level for a month. If treatment is given again before the number of cells have remained for some time at their original level, leukopenia of a greater degree and duration is produced than after the first treatment.

The fall in the lymphocytes is greatest in the first twenty-four hours, but they continue to drop for about three days. These cells rise with the white count, but do so proportionately more slowly. Subsequent treatments may keep the lymphocytes fewer in proportion to the white count than following the first irradiation.

5. The new short-wave-length roentgen-ray therapy, suitably given, produces no changes in the blood that are of a different character from those occurring after milder yet intensive irradiation.

However, it does produce more rapid, marked and persistent changes than milder treatment, and if the treatment consists of merely moderate long-wave exposures it may not even cause a decrease of white cells.

6. An eosinophilia, of often 7 and as high as 23 per cent, is usual two to three weeks after short-wave-length irradiation. It appears to develop particularly following repeated exposures.

7. After irradiation the blood contains many degenerated white cells, especially in the first three days. There is scant mention in the literature of this feature of the blood in man. Larger doses produce greater numbers of these cells than smaller doses. After short-wave-length therapeutic irradiations the degenerated cells often amount to 25 per 100 formed white cells.

8. Some increase of immature white cells may be observed, especially at about the time the white count begins to rise, after large doses of irradiation.

9. A slight increase of the platelets soon after irradiation is common. They are depressed less readily than the white cells, but following the transient rise they are often found slightly decreased and rarely markedly. Combined with leukopenia they may be an indication of greater marrow depression than a decrease of only the bone-marrow white cells. About four days after intensive irradiation and prior to a definite rise in the white count, the platelets rapidly increase and remain elevated above normal for days to weeks.

✓ 10. Important changes in the count of the red blood corpuscles and hemoglobin percentage do not occur as a result of mild or intensive therapeutic irradiation. Changes in the numbers of immature cells occur.

11. The clinical condition of the patient will influence the degree and duration of the blood changes after irradiation, but anemia *per se* does not seem to be of any great importance. The white cells of patients whose clinical condition is similar, given the same dose in the same manner, show considerable variation. On the average, patients with higher white counts before irradiation will develop leukopenia and marked lymphopenia less often than those with lower counts.

12. Much more important than the condition of the patient in determining the influence of irradiation on the blood is the size, intensity and character of the dose; larger doses producing greater blood changes than smaller ones.

13. The amount of surface area irradiated is a factor of great importance in determining the degree and duration of the decrease of white cells. The greater the surface area exposed to a given amount of irradiation the more profound, on the average, is the effect on the white cells. Secondary radiation, which is greater with larger than smaller doses, with short wave than long wave

lengths, and with a larger than a smaller portal of entry, probably plays a role in the production of the blood changes.

14. Depression of the activity of lymphatic tissue and bone-marrow are probably undesirable states, yet may occur for even weeks after irradiation without any obvious detrimental effect. In spite of the production of leukopenia and lymphopenia, the benefits derived from radiation appear to offset these changes.

15. Prior to irradiation, particularly if one dose has been given, the blood should be examined. A white count alone will usually suffice to indicate the state of the hemopoietic organs. If 5000 per cu. mm. or more, irradiation may be given without producing serious harm to the blood forming tissues. It is not ideal to give irradiation when leukopenia is present, but it may be done without disaster. With leukopenia, especially when marked, repetition of treatment probably becomes a more serious event.

16. Before treatment is given to a patient with leukopenia, a complete study of the formed blood elements should be made, for it may reveal a greater degree of marrow depression than that shown by leukopenia only, and thus induce one to decide against irradiation. In order to determine whether or not to treat a patient with a given degree of leukopenia, one must decide whether the benefits of treatment will offset the disadvantages of an increased depression of the hemopoietic tissue. This latter condition may become of relatively little importance and be distinctly less harmful than permitting a lesion to go untreated.

BIBLIOGRAPHY.

(The starred references are particularly serviceable.)

1. Aschenheim, E.: Der Einfluss der Sonnenstrahlen auf die leukocytäre Blutzusammensetzung, *Ztschr. f. Kinderh.*, 1913, 9, 87.
2. Aschenheim, E., and Meyer, S.: Der Einfluss der Lichtes auf das Blut, *Ztschr. f. exper. Pathol. u. Therap.*, 1921, 22, 22.
3. Aubertin, C.: Modifications du sang chez les radiologues professionnels, *Compt. rend. de la Soc. de biol.*, 1912, 72, 84.
- * 4. Aubertin, C., and Beaujard, E.: (a) Action des rayons x sur le sang et la moelle osseuse, *Arch. de méd. exper. et d'anat. path.*, 1908, 20, 273; (b) Action des rayons x sur le sang et les organes hématopoiétiques, *Compt. rend. de la Soc. de biol.*, 1905, 58, 217 and 1908, 64, 410, 437.
5. Aubertin, C., and Delamarre, A.: Action du radium sur le sang, *Compt. rend. de la Soc. de biol.*, 1908, 64, 437.
6. Barlow, Russ and Chambers: Radium in the Treatment of Malignant Disease, *Med. Res. Council. Special Report*, 1922, Series No. 62, p. 12.
7. Benjamin, E., v. Reuss, H., Sluka, E., and Schwarz, G.: Beiträge zur Frage der Einwirkung der Röntgenstrahlen auf das Blut, *Wien. klin. Wchnschr.*, 1906, 19, 788.
8. Brill, O., and Zehner, L.: Ueber die Wirkungen von Injektionen löslicher Radiumsalze auf das Blutbild, *Berl. klin. Wchnschr.*, 1912, 49, 1261.
9. Bucky, G., and Guggenheimer, H.: (a) Steigerung der Knochenmarksfunktion durch Röntgenreizdosen, *Berl. klin. Wchnschr.*, 1922, 1, 11; (b) Steigerung der Knochenmarksfunktion durch Roentgen reizdosen, *Klin. Wchnschr.*, 1922, 1, 11.
- ✓ 10. Case, J. T.: The New Short Wave Length Roentgen-ray Therapy, *Jour. Am. Med. Assn.*, 1922, 79, 699.

11. Case, J. T.: Technical and Clinical Aspects of the New Deep Roentgenotherapy, *Am. Jour. Roentgenol.*, 1922, 9, 530.
12. Cavazzeni and Minelli: The Autopsy of a Radiologist, *Arch. Roentgen-ray*, 1914, 18, 393 (abstract).
13. Chambers, H., and Russ, S.: The Action of Radium Radiations upon Some of the Main Constituents of the Normal Blood, *Proc. Roy. Soc. London (B.)*, 1911, 84, 124.
14. Clark, J. H.: Action of Light on Leukocyte Count, *Am. Jour. Hyg.*, 1921, 1, 39.
15. Cluzet and Chavelier: Action de l'émanations du thorium en inhalation sur les éléments figurés du sang, *Compt. rend. Soc. biol.*, 1922, 86, 432.
- * 16. Colwell, H., and Russ, S.: Radium, X-rays and the Living Cell, with Physical Introduction, Bell & Sons, London, 1915, p. 176.
17. Da Silva, Mello A.: Effects of Radioactivity on the Blood, *Arch. Brasileiros de Med.*, 1919, 9, 123.
18. Drinker, C. K.: The Pathological Physiology of Blood Cell Formation and Blood Cell Destruction, *Oxford Med.*, 1920, 2, 509.
19. Duke, W. W.: Variation in the Platelet Count, *Jour. Am. Med. Assn.*, 1915, 65, 1600.
20. Hauenstein, J.: Blut und Stoffwechseluntersuchungen bei Radiumbestrahlung, *München. med. Wchnschr.*, 1921, 68, 809.
- * 21. Heim, K.: Blutveränderungen bei der Grossfelderbestrahlung, *Arch. f. Gynäk.*, 1922-1923, 116, 291.
- * 22. Heineke, H.: (a) Ueber die Einwirkung der Röntgenstrahlen auf innere Organe, *München. med. Wchnschr.*, 1904, 51, 785; (b) Experimentelle Untersuchungen über die Einwirkung der Röntgenstrahlen auf innere Organe, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1905, 14, 21; (c) Experimentelle Untersuchungen über die Einwirkung der Röntgenstrahlen auf das Knochenmark, nebst einigen Bemerkungen über die Röntgentherapie der Leukämie und Pseudoleukämie und des Sarcoms, *Deutsch. Ztschr. f. Chir.*, 1905, 78, 196.
23. Hektoen, L.: Further Studies on the Effects of the Roentgen-ray on Antibody Production, *Jour. Infect. Dis.*, 1918, 22, 28.
24. Helber, E., and Linser, P.: Experimentelle Untersuchungen über die Einwirkung der Röntgenstrahlen auf das Blut, *München. med. Wchnschr.*, 1905, 52, 689.
25. Henri, V., and Mayer, A.: Action des radiations du radium sur l'hémoglobine; transformation en méthémoglobine, *Compt. rend. Soc. de biol.*, 1903, 64, 1412.
26. Hussey, R. G.: The Influence of X-rays on the Properties of the Blood, *Jour. Gen. Physiol.*, 1921-1922, 4, 511.
27. Koenigsfeld, H.: Study upon the Blood Changes Due to Artificial Sunlight, *Polska Gaz. Lek.*, 1922, 1, 12.
28. Kehrler, E.: Biological Changes from Roentgen Irradiation, *Zentralbl. f. Gynäkol.*, 1923, 47, 1171.
- ✓ 29. Larkins, F. E.: Acute Aplastic Anemia, *Lancet*, 1921, 1, 801.
30. Lazarus-Barlow, W. S.: On the Histology and Some Other Changes Produced in Animals by Exposure to the Gamma Rays of Radium, Medical Research Council Special Report, Series 62, 1922, p. 33.
31. Leitch, A.: The Immediate Effects of X-ray on the Blood Lymphocytes, *Arch. Radiol. and Electrother.*, 1921, 26, 122.
- * 32. Levin, I.: Action of Radium and X-rays on the Blood and Blood-forming Organs, *Am. Jour. Roentgenol.*, 1922, 9, 112.
- * 33. Lommel, F.: Stoffwechseluntersuchungen an Tieren bei tödtlicher Röntgenbestrahlung, *Med. Klin.*, Berlin, 1907, 3, 759.
34. Mackee, G. M.: X-rays and Radium in the Treatment of Diseases of the Skin, Lea & Febiger, Philadelphia, 1921, p. 209.
- * 35. Masieri, N.: Influenza della Röntgentherapie sulla composizione morfologica del sangue, *Gazz. d. osp.*, 1921, 42, 962.
36. Milchner, R., and Mosse, M.: Zur Frage der Behandlung der Blutkrankheiten mit Röntgenstrahlen, *Berl. klin. Wchnschr.*, 1904, 41, 1267.
37. Millet, J., and Mueller, T.: Some Phases of Radium Action with Special Reference to the Hematopoietic System, *Jour. Cancer Res.*, 1918, 3, 127.
- ✓ 38. Morris, R.: Action of the Roentgen-rays upon the Blood: an Experimental Study, *Am. Med.*, 1905, 10, 946.
39. Mottram, J. C.: (a) Histological Changes in the Bone-marrow of Rats Exposed to the Gamma Radiations from Radium, *Arch. Radiol. and Electrother.*, 1920, 25, 197; (b) The Red Cell Blood Content of Those Handling Radium for

Therapeutic Purposes, Arch. Radiol. and Electrother., 1920, 25, 194; (c) The Effect of Increased Protection from Radiation upon the Blood Condition of Radium Workers, Arch. Radiol. and Electrother., 1921, 25, 368; (d) Observations upon the Action of Radium and X-rays on the Mononuclear Leukocytes of the Blood of Rats, Proc. Roy. Soc. Med. (Sect. Pathol.), 1922, 15, 1; (e) Radium: Its Effect on Blood Platelets, Proc. Roy. Soc. Med., January, 1923, p. 9.

40. Mottram, J. C., and Clarke, J. R.: The Leukocytic Blood-Content of Those Handling Radium for Therapeutic Purposes, Arch. Radiol. and Electrother., 1920, 24, 345.

41. Mottram, J. C., and Russ, S.: Lymphopenia following Exposures of Rats to "Soft X-rays and the B-rays of Radium," Jour. Exper. Med., 1921, 34, 271.

42. Mouquin, M.: Action of Deep Roentgen Radiation on the Blood, Médecine, 1923, 4, 473.

43. Murphy, J. B.: Heteroplastic Tissue Grafting Effected through Roentgen-ray Lymphoid Destruction, Jour. Am. Med. Assn., 1914, 62, 1459.

44. Murphy, J. B., and Ellis, A. W. M.: Experiments on the Role of Lymphoid Tissue in the Resistance to Experimental Tuberculosis in Mice, Jour. Exper. Med., 1914, 20, 397.

45. Murphy, J. B., Liu, J. H., and Sturn, E.: Studies on X-ray Effects: IX. The Action of Serum from X-rayed Animals on Lymphoid Cells *in Vitro*, Jour. Exper. Med., 1922, 35, 373.

46. Murphy, J. B., and Morton, J. J.: The Effect of Roentgen-rays on the Rate of Growth of Spontaneous Tumors in Mice, Jour. Exper. Med., 1915, 22, 800.

47. Nakahara, W., and Murphy, J. B.: Changes in the Lymphoid Organs after Small Doses of X-rays, Jour. Exper. Med., 1919, 29, 83.

* 48. Nakahara, W., and Murphy, J. B.: The Biological Action of Small Doses of Low Frequency X-rays, Jour. Exper. Med., 1922, 35, 475.

49. Nurnberger, L.: Klinische Blutuntersuchungen bei der gynäkologischen Tiefentherapie, Deutsch. med. Wchnschr., 1915, 41, 730.

50. Petersen, W. F., and Saelhof, C. C.: Selective Organ Stimulation by Roentgen-rays; Enzyme Mobilization, Am. Jour. Roentgenol., 1921, 8, 175.

✓ 51. Pfahler, G. E.: The Effects of X-rays and Radium on the Blood and General Health of Radiologists, Am. Jour. Roentgenol., 1922, 9, 647.

52. Pinch, A. E. H.: Annual Report of London Radium Institute, Jour. Am. Med. Assn., 1922, 78, 985.

✓ 53. Portis, M. M.: Blood Changes in Workers with the Roentgen-ray, and Apparatus for Protection, Preliminary Report, Jour. Am. Med. Assn., 1915, 65, 20.

54. Proescher, F., and Almquest, B. R.: Résumé of the Effect of Soluble Radium Salts on the Circulating Blood Cells of White Mice and White Rats, Radium, 1914, 3, 85.

55. Rowntree, L. G., and Baetjer, W. A.: Radium in Internal Medicine: Its Physiologic and Pharmacologic Effects, Jour. Am. Med. Assn., 1913, 61, 1438.

56. Russ, S.: The Immediate Effect of X-rays on the Blood Lymphocytes, Arch. Radiol. and Electrother., 1921, 26, 146.

57. Russ, S.: Some Contrasts in the Effects of X-rays and Radium upon Blood Cells, Brit. Med. Jour., 1921, 2, 268.

58. Russ, S., Chambers, H., Scott, G. M., and Mottram, J. C.: Experimental Studies with Small Doses of X-rays, Lancet, 1919, 196, 692.

59. Russ, S., Chambers, H., and Scott, G. M.: Further Observations of the Effects of X-rays upon Lymphocytes, Arch. Radiol. and Electrother., 1921, 25, 377.

60. Schweitzer, B.: Veränderungen am Blute nach Mesothoriumbestrahlungen, München. med. Wchnschr., 1916, 63, 341.

✓ 61. Schroeder, J. H.: Intensive Deep Roentgen Irradiation, Jour. Am. Med. Assn., 1922, 79, 1240.

✓ 62. Stephens, R. H.: Blood in Cancer under Roentgen-therapy, Jour. Am. Med. Assn., 1916, 17, 1549.

63. Tatarsky, A.: Experimentelle Untersuchungen über die Einwirkung der Röntgenstrahlen auf tierisches Blut, Ztschr. f. med. Elektrol. u. Roentgenk., 1907, 9, 1.

64. Taylor, H. D.: Effect of Exposure to the Sun on the Circulating Lymphocytes in Man, Jour. Exper. Med., 1919, 29, 41.

65. Taylor, H. D., Witherbee, W. D., and Murphy, J. B.: Studies on X-ray Effects: I. Destructive Action on Blood Cells, Jour. Exper. Med., 1919, 29, 53.

66. Thomas, M. M., Taylor, H. D., and Witherbee, W. D.: Studies on X-ray Effects: II. Stimulative Action on the Lymphocytes, Jour. Exper. Med., 1919, 29, 75.

67. von Jagie, N., Schwartz, G., von Siebenrock, L.: Blutbefunde bei Röntgenologen, Berl. klin. Wchnschr., 1911, 48, 1220.
68. Warthin, A. S.: An Experimental Study of the Effects of Roentgen-rays upon the Blood-forming Organs, with Special Reference to the Treatment of Leukemia, Int. Clin., Philadelphia, 1906, 4, 243.
69. Westman, A.: Altérations du sang chez les malades traités par les rayons X et par le radium, Acta radiolog., 1921-1922, 1, 349.
- * 70. Wetterer, I. and Nemnick: Handbuch der Roentgen und Radium Therapie, Munchen-Leipzig, 1919, (vol. 1).

ADDITIONAL REFERENCES.

1. Desjardins, A., and Marquis, W.: Blood Counts and Blood-pressure in High Voltage Therapy, Radiology, 1924, 2, 252.
2. Falconer, E., Morris, L. and Ruggles, H.: Effect of Roentgen Rays on Bone Marrow, Am. Jour. Roent. and Radium Therapy, 1924, 11, 311
3. Klasten, E.: Ueber biologische Veränderungen nach Roentgenschwachbestrahlung bei einigen gynäkologischen Erkrankungen, Zentralbl. f. Gynäk., 1923, 47, 1174.
4. Mouquin, M.: Les modifications du sang à la suite de la radiotherapie pénétante, Médecine, 1923, 4, 473.
5. Trémolières, F., Colombier, P. and Aris, P.: Les variations de la formule hemoleucocytaire au cours du traitement de la tuberculose pulmonaire par la radiotherapie indirecte, Presse Med., 1923, 31, 417.
6. Vianello, C.: Ricerche sulle modificazione nel numero e nella formula degli elementi del sangue determinate dalla deboli dosi di raggi x sulla milza, Radiologia Med., 1923, 10, 139.
7. Watanabe, M., and Harrada, Y.: The Influence of Roentgen-rays on Hematopoiesis, Jap. Med. World, 1922, 2, 234.
8. Zweifel, E.: Zur Frage der Milzreizbestrahlung, Münch. med. Wchnschr., 1923, 70, 670.

PRIMARY CARCINOMA OF THE LIVER.

BY B. M. FRIED, M.D.,

BOSTON.

(From the Department of Pathology, Harvard University Medical School and the Pathological Laboratory of the Peter Bent Brigham Hospital.)

IN 1876 Kelsh and Kiener¹ reported 2 cases of primary carcinoma of the liver, and at that time found only one other case in the literature. Next Sabourin² added 4 more cases, but the first thorough investigation on the subject was done by Hanot and Gilbert³ in 1888.

According to the gross appearance, the French pathologists classified the tumor as:

1. "Cancer Nodulaire," in which the liver contains several tumor nodules varying in size and generally well circumscribed.
2. "Cancer Massif," in which the tumor consists of one large mass occasionally associated with metastases.
3. "Cancer avec Cirrhose."

Eggel⁴ in an investigation of 163 cases accepts the same macroscopical classification except for the "cancer avec cirrhose" which

he calls "cancer à forme diffuse" on the ground that cirrhosis is often found in the nodular as well as in the massive form.

Histologically, Eggel⁴ classifies each of these groups into the solid and adenomatous carcinomas. Ribbert⁵ differentiates trabecular and alveolar types. Goldzieher and Bokay⁶ divide the tumor into "Carcinoma Hepatocellulare" and "Carcinoma Cholangiocellulare" according to the cells from which they arise; viz., liver cells or epithelium of the smaller bile ducts. This nomenclature was later modified by Yamagiwa⁷ as "Hepatoma"* and "Cholangioma."

The incidence of the tumor is rare. Eggel⁴ in a review of the literature up to 1901 reported 163 cases and 1 case of his own. Among the 163, only 117 were studied histologically. In 258 cases of cancer of the liver, Hanseemann⁸ found 4 in which the liver was the primary seat of the tumor, Goldzieher and Bokay⁶ reviewed (1911) 6000 autopsies at the Pathological Institute of Budapest and found 18 primary cancers with an incidence of 0.3 per cent. (The highest figure ever reported.) Winternitz⁹ discovered at the Johns Hopkins Hospital only 3 cases of primary cancer of the liver in 3700 autopsies, an incidence of 0.028 per cent. Recently, Clawson and Cabot¹⁰ reported 1 case which is the only one in a total of 5100 necropsies performed at the University of Minnesota. At the Peter Bent Brigham Hospital, we found 4 primary carcinomas (3 cholangiomas and 1 hepatoma) of the liver in 1200 autopsies performed in the past ten years. At the Harvard Medical School only 1 case (cholangioma) has been seen in autopsies.

The cases reported were referred to me by Dr. S. B. Wolbach and belong either to the Harvard Medical School or to the Peter Bent Brigham Hospital. I desire to express my deep gratitude to Dr. Wolbach for his permission to study the cases, his kind suggestions, and criticisms.

Case Histories. CASE I.—CLINICAL HISTORY. S. H., a female, aged sixty-three years, entered the Peter Bent Brigham Hospital complaining of swelling of the abdomen with pain.

Family and Past History. Not remarkable.

Present Illness. Five weeks ago she noticed that her abdomen began to swell, accompanied by severe pain all over the abdomen and constipation. During this time she lost weight, and two weeks ago there was swelling of the legs and shortness of breath, and recently nausea and vomiting.

Physical Examination. Shows dulness at the bases of both lungs with diminished vesicular breathing on the left side and diminished bronchial breathing on the right side. There are numerous rales at both bases. The abdomen is tremendously dis-

* The term "hepatoma" was originally employed by the French writers, Rénon, Girouel and Monier-Vinard in the article *L'hépatome tumeur primitive du foie*, Arch. de méd. expér., 1910, 22, 311.

tended. There is marked edema of the legs and the lower half of the trunk. Pelvic and rectal examinations are negative.

The patient was tapped twice, 5000 cc and 4100 cc of fluid being obtained. The specific gravity of the fluid was 1008 and a differential count showed 352 cells, 7 per cent of which were polymorphonuclear leukocytes and 85 per cent lymphocytes. The blood Wassermann was double plus. The leukocytes were 19,000 per c.mm.

Clinical Diagnosis: Cirrhosis of liver, probably luetic.

Autopsy (A-21-118) was performed by Dr. S. B. Wolbach and Dr. W. S. Quinland.

Body: Not remarkable on general inspection, except for a protuberant abdomen and the presence of two paracentesis wounds in the median line and in the right flank respectively.

Peritoneal Cavity: Contains 1800 cc of bile tinged fluid in which are several flecks of fibrin that measure roughly 4 to 5 cm. in length. This fluid when stained is found to contain endothelial cells and polymorphonuclear leukocytes with a few phagocyted bacilli having the morphology of colon bacilli. There are a few fibrous adhesions in the region of the ileocecal junction. The appendix is very small and appears to be somewhat atrophic. It is bound down posteriorly to the cecum by fibrous adhesions. The height of the diaphragm reaches the lower border of the fifth rib on the left and the fourth rib on the right. The mesenteric lymph nodes are not remarkable.

The pleural and pericardial cavities are not remarkable.

The heart weighs 260 gm. and except for a tortuosity of the vessels is not unusual.

The lungs weigh (right) 390 gm. and (left) 330 gm. They are similar in appearance, and except for a hypostatic congestion are not remarkable. Along the surface and adjacent to the interlobar septa on the right and the interlobar septum on the left are a few whitish elevations in what appears to be lymphatic vessels that suggest tumor metastases.

The spleen weighs 210 gm. and shows chronic passive congestion.

Gastrointestinal tract: The stomach contains about 16 cc of "coffee-ground" material. The mucosa has a few pin-head sized areas of depression, suggestive of autodigestion. At a distance of 5.5 cm. from the pyloric orifice in the duodenum is a definite ulcer of about 7 mm. in diameter, the base of which rests on the head of the pancreas. The borders are regular and smooth, and the surface in general appears dark red. In this same region but on the anterior wall of the duodenum is a similar ulcer that has perforated the wall of the gut.

The pancreas is normal.

The liver weighs 1820 gm. and is practically replaced by a tumor which is more evident in the left lobe. Here the liver tissue is entirely replaced by tumor and the organ in this region is dense

and of cartilaginous consistency. Toward the mesial portion, patches of liver tissue are seen that measure roughly 3 cm. in diameter and on the under surface of the right lobe the largest patch of liver tissue is seen (about 10 cm. in diameter). The surface of the organ is irregularly indented, the tissue being pulled down, having little wrinkles on the surface. On section the appearance is well mottled in the right portion but more homogeneous on the left side where the tumor is more diffuse.

The gall-bladder is normal and the ducts are patent.

The kidneys are similar in appearance. The right weighs 130 gm. and the left 140 gm. The capsule strips easily from both organs, leaving a dark red, finely granular surface. On section through the left kidney a few pin-head sized tumor metastases are seen in the region of the medulla. The cortex is regular and appears normal. The glomeruli and pelves are normal.

The adrenals are normal.

The bladder is normal.

Except for a small fibroid the uterus is not remarkable, the ovaries and tubes are of the senile type.

The aorta shows a few atheromatous plaques in the abdominal portion.

The thyroid and parathyroid glands are dissected after the tongue and trachea have been removed. No evidence of tumor is observed.

Microscopical Examination. Liver: Sections are stained with methylene blue-eosin, with phosphotungstic acid-hematoxylin and with Mallory's anilin blue. They all show areas of tumor consisting of cuboidal epithelial cells. The cytoplasm of the cells is stained with a basic stain, is clear and is not abundant. The nucleus is ovoid or round, vesicular and contains a deeply stained nucleolus. The arrangement of the cells is in general adenomatous with a tendency to form small ducts. The larger masses of tumor seem to be generally confined to the portal areas and it is from these areas that they spread and extend into the liver substance. In the center of some tumor masses, the bile duct of the portal area can still be made out. In general, the portal areas contain an increased amount of fibrous tissue which is dense around the bile ducts. The latter are everywhere hyperplastic, their lining epithelium being of a tall variety, and in areas consisting of 3 to 4 rows, forming folds into the lumen. Tumor growth is present in the capillaries in the portal areas. Mitotic figures are frequent. The stroma of the tumor in the large as well as in the smaller nodules consists of connective tissue which in areas is very abundant.

The tumor ends rather diffusely in the surrounding liver substance which shows a marked distention of the sinusoids by serum and red cells (edema and congestion). The liver cells themselves being arranged normally show, however, some changes; their nuclei are pyknotic in proximity to the tumor and the cells are compressed and atrophic.

Lungs: The tumor here is made up of the same type of cells and has a similar arrangement as in the liver. It is located in the interlobar septa and in some perivascular spaces. The stroma is fibrous. The adjacent normal lung substance is compressed. There is congestion and a moderate amount of anthracosis. The bronchioles are not remarkable.

Spleen: The histology is that of a chronic congestion.

Pancreas: Shows polymorphonuclear leukocyte infiltration of the interlobar septa and lobules. A few thrombosed vessels are seen. There is no evidence of tumor.

Duodenum: Sections show in one portion necrosis of the mucosa and submucosa with very little inflammatory reaction. A few polymorphonuclear leukocytes are seen in the muscle coat. The stomach is normal.

Kidneys: Sections show congestion and an accumulation of blood in some of the straight tubules. One of the sections shows a circumscribed area of scarring in which epithelial cells are scattered loosely. There is a slight thickening and retraction of the glomerular tufts, also a few areas of scarring in the cortex.

Adrenals: Normal.

Genitalia: Normal.

Thyroids and parathyroids: Normal.

Microscopical Diagnosis. Carcinoma of liver with metastases to lungs and kidneys; ascites; duodenal ulcer, perforating; chronic passive congestion of spleen; edema of extremities; arteriosclerosis.

CASE II.*—CLINICAL HISTORY. E. P., an unmarried seamstress, aged sixty-one years, entered the Peter Bent Brigham Hospital complaining of an increasing sense of "tightness" in the chest, some "wheezing" on breathing, progressive dyspnea, occasional slight hemoptysis and insomnia. Associated with these complaints were increasing weakness and loss of weight of about 20 pounds. According to her statement she had been sick for one month.

Family History. Her father and both paternal grandparents died in middle age of pulmonary tuberculosis.

Past History. She had had measles at six, "intermittent fever" at sixteen, and malaria at forty-six; hysterectomy and oöphorectomy ten years ago, following vague pelvic symptoms. She was told that gall stones were found in her gall-bladder, but that her condition prevented further investigation.

Physical Examination. The chest showed questionable small areas of dulness posteriorly, most marked in the region of the hila. Fine crepitant rales were heard through the left lung and there were a few fine moist rales at the right base, behind and over the right lower chest anteriorly. The abdomen is negative, except for an

* This case was reported from the clinical point of view by R. M. McKean in *AMER. JOUR. OF MED. SCI.*, 1922, 163, 710.

increased resistance to palpation in the epigastrium and right hypochondrium. An underlying mass, the character of which could not be determined on account of the rigidity of the abdominal musculature. The liver dulness extended from the sixth rib above to three finger breadths below the costal margin.

Heart, Gall-bladder, Spleen and Kidneys. Not remarkable.

Roentgen-ray showed a "spotty" consolidation throughout both lungs, most marked in the lower lobes. This consolidation has every appearance of being metastatic malignancy and not tuberculosis. The blood Wassermann was negative. Gastric analysis showed a normal acidity curve. The sputum was repeatedly negative for tubercle bacilli. Stool and urine examinations were negative. The patient remained in the hospital for forty-seven days and died apparently of respiratory failure.

Clinical Diagnosis. Metastatic malignancy of the liver and lungs. Primary source undiscovered.

Autopsy (A-20-108) was performed by Dr. V. Jacobson.

General examination of the body is negative.

There is no free fluid in the peritoneal cavity. The omentum is firmly adherent to the peritoneum along the line of the abdominal scar. The liver is very prominent, being pushed downward and forward, its lower border being 15.5 cm. below the xyphoid cartilage and 7 cm. below the right costal margin. The spleen is covered by the left lower ribs. The appendix is not present. A short cervical stump remains. The diaphragm is on a level with the lower border of the third rib on the right and with the fourth rib of the left. The mesenteric lymph nodes are very small and are embedded in much mesenteric fat.

The pleural cavities are almost obliterated by the adhesion of the lungs to the parietal pleura which is rough and nodular, due to the presence of innumerable, irregularly rounded projections of tumor, varying in size from a pin-head to one on the diaphragmatic pleura which is 3 x 2 x 3 cm. These nodules are dark red, streaked with white, very firm and unusually surrounded by radiating dilated veins. In the right cavity, 250 cc of blood-tinged fluid and in the left 150 cc of similar fluid is found.

In the mediastinum, the under surface of the sternum is studded with tumor nodules 0.2 to 2 cm. in size. The mediastinal fat is of normal amount and shows no tumor growth. The organs are in normal position.

The pericardial cavity and heart are normal.

The lungs weigh (right) 710 gm. and (left) 705 gm. They are quite similar in appearance, about half the normal size, but much increased in weight. The pleural surfaces are rough and nodular, due to the presence of innumerable, rather hard, pale white, circumscribed growths, varying in size from 1 mm. to 2 cm., projecting about 3 mm. above the surface. They are found all over the pleura, and while

the lymphatics are fairly prominent, these tumors do not seem to be intimately connected with them and about many are radiating, dilated venules. Between these bodies the tissue is rather elastic and is slightly crepitant and grayish-red. The glands at the hili and also at the bifurcation of the trachea are 1 to 2 cm. in size, many are very firm and on section are opaque white, streaked with red. A lateral incision in each lung shows a widespread distribution of tumor nodules, similar to those on the pleural surfaces. They vary in size as in the pleura and are diffusely distributed in the lung lobules. Many are stained with carbon pigment or surrounded by a narrow black ring of anthracosis. The tissue between the tumor varies in color from gray to deep red and in consistency from elastic to firm and meaty. Thrombi occlude many of the arterioles but the larger vessels are empty. In some of the bronchioles are dark red blood clots in which are small particles of opaque white tissue suggesting tumor. The trachea shows moderate injection of the mucosa.

The liver weighs 2360 gm. It is much enlarged, particularly its right lobe, which on its lateral and posterior surfaces is firmly adherent to the diaphragm. This is due to the presence of a tumor mass occupying about half of the right lobe and extending outward so that a mass with pearly white, raised borders and dark red, depressed central portion projects about 1 cm. above the surface over an area about 12 cm. in diameter, forming a growth, shaped more or less like a group of rosettes. The diaphragm appears to be invaded, and streaks of grayish-white tumor tissue run from the liver tumor to the large nodules on the pleural surface of the diaphragm.

Sections of the liver at various angles show that the gross tumor is limited to the large mass in the right lobe, the rest of the organ having only a moderate "nutmeg" appearance. It is fairly well circumscribed and its greatest diameter is 15 cm. It is of almost cartilaginous hardness and has no definite capsule, though with rounded edges. There is distortion of the liver lobules adjoining it, probable due to pressure. The tumor is not bile stained and there is no gross evidence of bile stasis. Dissection of the larger bile ducts leading to the tumor is abruptly stopped when the tumor is reached. Small branches of the hepatic vein contain thrombi in the vicinity of the tumor, and a few of them contain flecks of grayish-white, quite firm tissue, possibly tumor. The ducts and vessels of the rest of the liver show no lesions.

The gall-bladder is but 5 cm. from the tumor but its mucosa moves freely over the subjacent tissues and appears normal. Eight black facettted calculi, 1.5 cm. in size, lie free in the gall-bladder. The cystic, hepatic and common ducts in the porta hepatica show no stones or tumor. Two lymph glands at the junction of the cystic and hepatic duct are enlarged and firm, measuring 2 x 5 cm. in size, but are pale and do not appear to contain tumor.

The spleen weighs 220 gm. and shows chronic passive congestion. The kidneys each weigh 110 gm. and show passive congestion and arteriosclerotic changes.

The adrenals and bladder are normal.

Only the stump of the cervix uteri remains. (The patient had been operated upon for fibroids.) A red pedunculated polyp, 2 x 5 cm. is attached to the mid portion of the cervical mucosa and is bathed in a reddish mucoid secretion.

The aorta shows moderate arteriosclerosis.

The inferior vena cava contains no thrombi.

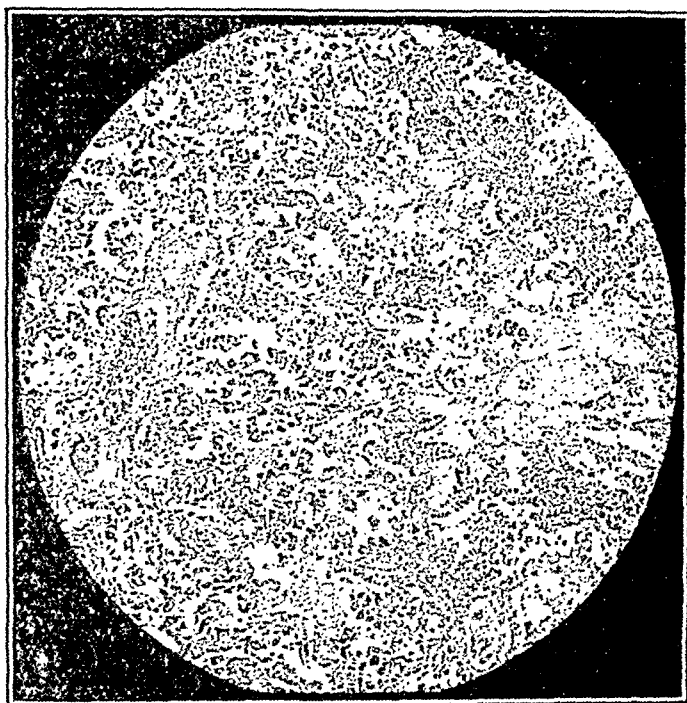


FIG. 1.—Case II. Cholangioma. $\times 70$.

Microscopical Examination. Liver: Thirty sections are stained with methylene blue-eosin with phosphotungstic acid-hematoxylin and with Mallory's anilin blue. They show tumor consisting of cylindrical or cuboidal cells with a narrow basic stained cytoplasm and a large finely granular nucleus resembling very much that of the bile ducts. The tendency of the cells is to arrange themselves in acini which vary markedly in size. Some of the acini have a small lumen filled with necrotic material, some others have their lumen filled with tumor cells. The stroma of the tumor varies markedly in different parts, from a dense fibrous tissue containing a few tumor cells to delicate strands supporting single rows and large columns of epithelial cells (Fig. 1).

In the portal areas there is a proliferation of fibrous tissue and bile ducts. Many of the latter have their epithelial lining several

layers thick, partially occluding the lumen, while in others the epithelial cells rupture the basement membrane and invade the surrounding tissue.

There is a pressure atrophy of many of the liver cells as a result of tumor invasion and marked congestion of the sinusoids. Isolated liver cells frequently appear necrotic. There are also foci of necrosis, most marked about the central areas with many "polys" in the adjacent sinusoids attracted, no doubt, by the necrotic liver cells. Liver cells show tremendous fatty infiltration. Two sections show no tumor but considerable fatty infiltration.

Lungs: The tumor in the lungs resembles the primary tumor. The sections show nests of epithelial cells surrounded by a connective tissue stroma and like the acini are lined by epithelial cells several layers in thickness. The structure is typical of an adenocarcinoma. The lung metastasis is more cellular than the primary tumor and has invaded alveoli in which masses of tumor cells are found. Mitotic figures are present.

The remaining portions of sections show congestion of the alveolar capillaries. Large numbers of desquamated epithelial cells and a few polymorphonuclear leukocytes and endothelial cells are seen in the alveoli. A few of these contain plugs of fibrin and invading fibroblasts. Sections from trachea and attached lymph nodes show no tumor.

Lymph Node (Bronchial): It is surrounded by a thick capsule and contains abundant coal pigment. The central portion shows an extensive invasion of tumor cells. The cells and their arrangement are similar to the tumor elsewhere.

Heart: The heart shows chronic fibrous myocarditis.

Spleen and Kidneys: Sections from these organs show a chronic passive congestion.

Pancreas: There is an acute hemorrhagic necrosis, probably agonal.

Bladder: An acute cystitis is present.

Aorta: A moderate amount of arteriosclerosis is present.

Inferior Vena Cava: No tumor is found.

Microscopical Diagnosis. Adenocarcinoma of liver (primary) with metastases to lung, pleura and bronchial lymph nodes. Pleural effusion. Acute hemorrhagic pancreatic necrosis. Chronic fibrous myocarditis. Cervical polyp. Diverticulum of bladder. Absence of uterus, tubes, ovaries and appendix (operative).

CASE III.—A. L., female, aged sixty-six and a half years. This case lacks a clinical history. The clinical diagnosis as given in the autopsy protocol is "Carcinoma of the liver." Autopsy (H-11-945) performed by Dr. E. E. Tyzzer. Twenty-four hours postmortem. The body is considerably emaciated, 155 cm. long, and postmortem lividity is present.

The pleural cavities contain no fluid and no adhesions.

The lungs are light and all portions contain air. The left apex shows a puckered scar-like area 2 by 3 cm. On palpation, numerous small nodules are felt which measure from 1 to 10 mm. A few of these are in contact with the pleura. On section, they are finely subdivided, the subdivision being of a uniform size and measuring not over 0.4 mm. in diameter. They are pale pink and of a firm consistency.

From the abdomen about 2 liters of cloudy, rather thick fluid has been drawn off by the embalmer. This fluid clotted spontaneously into a firm mass. At the present time, the peritoneal cavity contains a small amount of fluid with flecks and small masses of fibrinous purulent exudate. There is a mass of exudate upon the superior surface of the liver near the anterior border. There is also a collection of grayish, shiny exudate with masses of clotted fibrin in the region of the cecum. There is no demonstrable appendix, but this organ is represented by a thin, ragged membrane measuring 5 cm. in length. Adjacent to this in the wall of the cecum is a small pocket of pus about 7 cm. in diameter. The cecum is small, contracted and has a rigid tough wall. The mesenteric lymph nodes are not notably enlarged.

The spleen shows passive congestion.

The stomach is markedly dilated, with a capacity somewhat over 3 quarts. The mucous membrane is normal.

The small and large intestines appear normal.

The pancreas appears normal throughout. Lying against the head of the pancreas, occupying the space between this and the liver, are several nodules of tumor tissue, the largest of which measures 3 cm. The tumor does not appear to have arisen in the pancreas.

The liver weighs 3800 gm. and extends 3 cm. below the costal margin. The liver tissue is replaced to a large extent by tumor tissue. There are a few smaller nodules but the tumor forms a more or less continuous mass extending throughout the entire organ. The interior of the tumor is necrotic everywhere, and of caseous consistency, opaque and yellowish in color. The peripheral portions of the liver are about equally involved.

The gall-bladder is filled with dark fluid, slightly viscid bile in which are no calculi. The mucous membrane of this, as well as that of the duct, appears normal.

Both kidneys weigh 250 gm. The capsule strips readily, leaving a somewhat roughened, granular surface. The cortex measures 4 to 10 mm. and appears slightly opaque and of a brownish color.

The adrenals are normal.

The uterus is small and markedly atrophied. There are two small pedunculated tumors measuring 7 mm. on the peritoneal surface. The ovaries are senile. No tumor is present here.

The aorta shows many numerous areas of arteriosclerosis.

Microscopical Examination. Liver: The tumor in the liver is composed of epithelial cells having a tall cylindrical shape. The cytoplasm of the cells is clear and narrow and the nucleus vesicular, large, oval or round. The cells are arranged in a duct-like manner, the nuclei of which are pushed toward the periphery, and the small lumen filled with débris and necrotic material. In general, the cells and their arrangement resemble closely the bile ducts. Mitotic figures are present. The tumor is supported by a connective-tissue stroma which is more marked around the portal areas where it is fibrous. In the portal areas, the bile ducts seem to be increased in number and their lining epithelium is hyperplastic. There is also a marked lymphocytic infiltration. In some ducts the epithelium is desquamated and lies free in the lumen. There is much necrosis in the tumor. The liver substance surrounding the tumor is compressed and atrophic. The liver cells are also damaged in the parts remote from the tumor. The sinusoids are distended and filled with serum, blood and round cells.

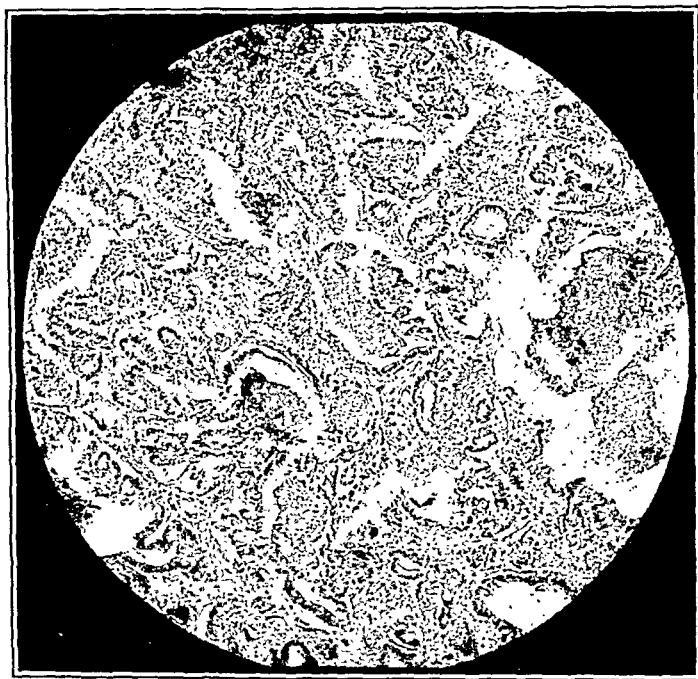


FIG. 2.—Case III. Cholangioma. Metastatic tumor in the lungs. $\times 70$.

Lungs: In one section the tumor is situated beneath the pleura and shows a striking similarity by the type of cells, and their arrangement to the primary tumor and consequently to the bile ducts. In the center, the lung markings are destroyed, and the fibrous stroma dominates the picture. At the periphery the tumor plugs the alveoli, the outline of which is still recognizable. The lumen of the acini here contains necrotic material (Fig. 2).

In another section taken from the center of the lung, the tumor acini have no lumen and are closely packed together being supported by a delicate connective-tissue stroma. At the periphery, here also the tumor fills the alveoli, the walls of which can be made out. The parts of the lung free from tumor show marked congestion of the capillaries of the alveolar wall, but otherwise are not remarkable. The bronchi are normal.

The spleen shows marked passive congestion.

Microscopical Diagnosis. Carcinoma of liver, metastatic to lungs. Chronic and acute appendicitis. General peritonitis. Slight chronic pleuritis. Arteriosclerosis. Slight chronic nephritis.

CASE IV.—CLINICAL HISTORY. M. H., female, single, a house-keeper, aged sixty-two years, entered the Peter Bent Brigham Hospital complaining of jaundice.

Family History. Not remarkable.

Past History. Forty years ago she underwent an operation on the uterus or ovaries followed by an artificial menopause.

Present Illness. She has always had good health until seven weeks ago, when she began to feel wretched, had fever and chills, and went to bed. The local doctor diagnosed "jaundice." She noticed her urine was highly colored and also noticed her stools were of a grayish color.

Physical Examination. An obese woman with slightly jaundiced scleræ, coarse rales at bases of lungs posteriorly, and a loud systolic murmur over the apex and at the base of the heart. A systolic thrill is felt over the aortic area. The cardiac rhythm is irregular. The abdomen is distended, and the liver enlarged, extending below the umbilicus.

The patient died after five days in the hospital.

Clinical Diagnosis. Malignancy of liver; auricular fibrillation; mitral stenosis.

Autopsy (A-23-72) was performed by Dr. Wilens.

The body is that of a fairly well-developed and well-nourished white female, measuring 152 cm. in length. The entire body is tinted a yellow color and the scleræ are markedly jaundiced.

In the peritoneal cavity are many strong fibrous adhesions, attaching together several coils of both small and large intestine to the parietal peritoneum.

In the pleural cavity the right lung is entirely bound down by old fibrous adhesions and is firmly attached to the right side of the pericardium. The left pleural cavity is normal.

The heart is normal.

The right lung weighs 600 gm. and after removal is still covered with the parietal pleura. The lung tissue stands out quite firmly in places, suggesting bronchopneumonia. In the middle lobe, on section, a white opaque nodule is seen which measures about 1 cm.

in diameter. It is definitely firm and suggests a metastatic growth. The left lung weighs 400 gm. and appears normal.

The liver weighs 3680 gm. It measures anteroposteriorly 27 cm., transversely 26 cm. and vertically 20 cm. The margins are round and the surface smooth, shiny and greenish. Throughout the skin capsule innumerable grayish nodules from 0.5 to 1 cm. in diameter are seen. A large grayish mass, consisting apparently of several small nodules, is present in the lower right quadrant. Except for this area where the liver is very firm, the organ is soft and has a rather spongy feeling. On examining the large vessels *in situ*, no tumor is discovered within them (Fig. 3).



FIG. 3.—Case IV. Cholangioma. Note also the foamy appearance of the liver due to *Bacillus welchii*.

On section, a tumor mass measuring 5 x 6 x 7 cm. is found situated in the lower right quadrant of the liver. The outline of the tumor is irregular and at the periphery it seems to be composed of several small nodules, while in the center it is uniformly gray and contains a mass of necrotic material.

The liver was cut in slices 1 to 1.5 cm. thick. The cut section showed tumor nodules 0.5 to 1 cm. in diameter to be scattered practically all over the organ. The tissue between the nodules is bile stained and has a typical foamy appearance due to the invasion of the body by gas bacillus (*B. welchii*).

On dissecting the vessels grayish pin-point elevations—apparently tumor—are seen in various places. In no instance are the smaller or larger vessels found to be plugged or to contain tumor masses of a considerable size.

The gall-bladder is definitely distended to the size of a pear and on opening it, three large stones measuring $2\frac{1}{2}$ cm. in diameter each are seen. The wall is markedly thickened but not inflamed. No ulceration or scars are found in the mucosa. Many smaller stones

are bathed in a thick mucous fluid. All of the stones are definitely black. The ducts are patent.

The heart weighs 320 gm. and is not remarkable.

The kidneys are normal.

The aorta shows arteriosclerosis of the ordinary type.

Microscopical Examination. Liver: Sections are taken from large and small nodules. The histology of various parts of the tumor is quite similar. The tumor cells both in appearance and arrangement closely resemble those of bile ducts. The cells are cylindrical or polygonal with a clear cytoplasm, and a round or oval vesicular nucleus, and a very deeply stained nucleolus. These cells are supported by a delicate connective-tissue stroma. In one section, the tumor invades a vein. There is much necrosis in the tumor. There is practically no normal liver tissue in the sections. Large areas represent either débris or extremely vacuolated cells. The portal areas are made out among the degenerated cells and the bile ducts in these areas are hyperplastic. A great many *B. welchii* are found in the sections.

Microscopical Diagnosis. Primary carcinoma of liver with metastases to right lung; arteriosclerosis; cholelithiasis; jaundice; fibrous pleurisy.

CASE V.—R. M., a German construction engineer, aged sixty-four years, married, entered the Peter Bent Brigham Hospital complaining of swelling of the abdomen.

Family History. Negative.

Past History. Heavy alcoholic addict in the past. Gonorrhea forty years ago. Syphilis thirty-eight years ago. Pneumonia twenty-eight years ago with complete recovery. Typhoid three years ago with complete recovery. Ten and a half years ago he had for about one year jaundice with clay-colored stools, and slight edema of the legs. During the past year, frequent epistaxis.

Present Illness. During the past year he has had attacks of progressive dyspnea on moderate exertion, and also attacks of palpitation, not associated with pain or dyspnea. Two months ago he vomited about one quart of blood and passed tarry stools. One week later (seven weeks ago), the abdomen and ankles began to swell, decreased for a time, but increased again about two weeks ago, with dull, constant pain in the lower abdomen. For two months his appetite has been poor, bowels very constipated and he has had excessive thirst and nocturia (2 to 3 times nightly).

Physical Examination. The patient is well nourished and well developed, with slight dyspnea and cyanosis and yellowish skin. The respirations are costo-abdominal in type. There is dulness and diminished tactile and vocal fremitus at both bases. Heart not remarkable. The systolic blood-pressure is 148, the diastolic 68. The abdomen is much distended, the abdominal wall markedly

edematous. The superficial abdominal veins are prominent and a fluid wave is present. There are no masses or tender areas. The upper border of the liver dulness is at the lower border of the fourth rib. There is edema of legs and thighs.

The patient was tapped twice and $15\frac{1}{2}$ liters of yellow opalescent fluid was obtained in a period of six days. He was discharged and was readmitted ten days later. On tapping again, 10 liters of fluid were obtained of the same character as previously described. He was again discharged and readmitted eighteen days later. Eleven and a half liters of chyloform like, turbid fluid was removed. He died on the twelfth day of the last admission.

Autopsy (A-22-103): The autopsy was performed by Dr. B. Reifenstein, nineteen hours postmortem.

The body is that of an exceedingly well-developed and well-nourished adult, white male, measuring 165 cm. in length. There is slight edema of the lower extremities and some slight jaundice of the face and neck. The scleræ are icteric. The abdomen is full, especially in the flanks and gives evidence of fluid. In the midline below the umbilicus are several small scars of previous paracenteses.

The peritoneal cavity contains about 2500 cc of clear straw colored fluid. There are no adhesions. The mesenteric lymph nodes are not enlarged. The peritoneum is grayish in color, smooth and glistening. The diaphragm extends to the fifth rib on both the right and left sides. The appendix is somewhat fibrous in character, and extends downward over the brim of the pelvis. The spleen is slightly enlarged, and there are a few adhesions to the diaphragm. The liver is atrophic, nodular and does not extend to the costal margin. The gall-bladder is distended with bile. The small and large intestines are negative to external examination. The bladder is distended with urine. The vein of the round ligament is markedly dilated and filled with blood clot.

The pleural cavities contain no free fluid. The left lung is free from adhesions. The right lung is markedly adherent to the pleura over practically all the surfaces of the lung. Palpation of both lungs reveals numerous hard, firm, nodules, some on the surface and some located deeper in the lung tissue. Both lungs appear voluminous.

The mediastinum and pericardial cavity are not remarkable.

The heart weighs 350 gm. The mitral valve is markedly thickened and has calcareous deposits 2 to 3 mm. in diameter along the margins of the cusps. The aortic valve and portions of the arch also show rather marked arteriosclerotic thickening.

The lungs weigh (right) 705 gm. and (left) 725 gm. Both lungs are crepitant throughout and vary from a grayish-white color on the anterior surfaces to a reddish discoloration in the dependent parts. The pleura of the right lung is rough and denuded, due to its difficult removal on account of rather firm adhesions. Palpation

of both lungs reveals scattered, firm discrete areas from 1 to 8 mm. in diameter. These firm areas are especially more numerous along the anterior borders of the lungs. They are irregular spherical in shape, while in certain places conglomerations are formed. On section, these areas are brownish-yellow in color, resembling liver tissue, are elevated from the cut surface, and appear to be rather sharply outlined from the surrounding normal lung tissue. Some of these areas are firm and hard, while others appear softer, almost puriform in nature. On dissection of the smaller arteries of both lungs, small grayish-pink thrombi are found. Some of these are adherent to the vessel wall. Smears show them to be made up of some epithelial cells and a few cocci in pairs. The bronchi are negative. Some of the bronchial lymph nodes are enlarged up to a diameter of 1 to 2 cm. On section, these are rather firm and show some pigmentation together with several small brownish areas which may be tumor metastases. Some of the tissue surrounding the tumor nodules appears firm and red in color, as if there is a beginning infectious process.

The spleen weighs 280 gm. The markings are distinct and there is no evidence of tumor.

The gastro-intestinal tract and pancreas are normal.

The liver weighs 1320 gm. The organ and its surrounding structures are examined *in situ*. The most impressive thing is the symmetrical decrease in the size of the liver, all portions being involved. The surface is roughly nodular and pale brown in color. The nodules vary from 0.2 to 0.5 cm. in diameter, and project from the surface. The liver is hard and stiff, shrunken and deformed. The surface is roughened all over by projecting nodules of a yellowish-brown color. The shrunken tissue between the nodules is gray and translucent. On the surface are seen several larger nodular areas, slightly red in appearance.

Inspection of the inferior surface of the liver reveals the dilated vein of the round ligament and also shows the portal vein to be markedly enlarged and somewhat firm in consistency. Palpation of the gall-bladder reveals gall stones. The cystic and hepatic ducts are dissected out and found to be patent throughout. The portal vein reveals a most remarkable picture. In places the entire lumen is filled with a reddish-gray, rather soft, friable, almost puriform material which is somewhat adherent to the intima. Where it is adherent to the intima, there is a marked thickening of the wall of the vein. Most of this material lies free in the vein. The portal vein is dissected down to the splenic tributary. The thrombus apparently extends to this point and cannot be traced into the splenic vein. The vein of the round ligament is next opened and found to contain the same material. The para-umbilical vein between this vein and the portal vein is markedly dilated and filled with the same thrombotic material. The portal vein is dissected

into the liver, and here it is filled with a yellowish-red, soft material resembling tumor tissue. The hepatic veins are opened above, and contain some of the same necrotic tumor thrombi.

On section (Fig. 4) the liver has a mosaic appearance of nodular masses 2 to 6 cm. in diameter, separated by a somewhat retracted, grayish-white tissue. However, in areas and especially in cut surfaces of the larger nodular masses noted on the surface, there are found irregular, spherical, reddish-brown and yellowish-brown, adenomatous areas resembling normal liver tissue. Some of these areas are rather soft, and a smear taken shows them to be practically all epithelial cells. There are multiple nodules scattered throughout the liver. Frozen section from one of these areas reveals carcinoma of the liver. The esophageal veins are dissected out, but present nothing unusual. The spermatic vein is found and is rather dilated, perhaps due to collateral circulation.



FIG. 4.—Case V. Hepatoma. T, tumor plugging the larger vessels.

The gall-bladder contains 10 stones about 1 cm. in diameter, each greenish in color and rather firm. The gall-bladder is not thickened. There are no scars or ulcerations in the mucosa.

The kidneys and adrenals show nothing remarkable.

The bladder contains bile-stained urine.

The prostate shows no evidence of tumor invasion.

The aorta is markedly involved by arteriosclerosis. There are numerous yellowish plaques, calcified areas, and several atheromatous ulcers.

The bone-marrow (femur) is composed of equal parts of red and yellow soft tissue rather characteristic of a secondary anemia.

Microscopical Examination. Liver: Sections are taken from tissue apparently free from tumor, and consisting only of sclerosed

liver substance, and also from tumor nodules. This is stained with methylene blue-eosin, Mallory's anilin-blue, phosphotungstic acid-hematoxylin and by Pedrou's silver-nitrate method. The usual lobular arrangement in this section has been destroyed and instead there are isolated masses of liver tissue of a different size and shape, surrounded by large bands of connective tissue which are infiltrated with small round cells. The columns of liver cells in these areas have no longer their usual radial arrangement toward the efferent vein, which in some nodules cannot be found at all and in others is situated near the periphery. The liver cells in these adenomatous areas are of a normal polygonal shape, with one round nucleus and a deeply stained nucleolus. The cytoplasm of the cells has an excessive granulation and a somewhat "foamy" appearance. The nuclei are pyknotic in areas. The sinusoids in these areas are dilated, but contain very little blood. Many of the cells contain bile pigments.

At the periphery of some of these nodules, liver cells of a larger size than usual, with a pale cytoplasm, containing in their nuclei a somewhat increased amount of chromatin are seen. Occasionally these cells are in mitosis and are apparently newly regenerated liver cells. In some areas small liver nodules consisting of normal liver cells are present.

The portal areas contain an increased number of bile ducts which occasionally have their normal rosette appearance, and in other places are enlarged and have a cleft-like lumen. Some of the bile ducts sprout into the lobules. The fibrous tissue from these areas often penetrates the adenomatous nodules. Some lobules are necrotic and can be made out only by the presence of a few liver cells at their periphery. In many other lobules the cytoplasm of the cells represents a homogenous mass, and the nucleus is in a stage of karyorrhexis and chromatolysis. Hemosiderin is present in large masses.

Tumor: Tumor replaces entire lobules in very few instances. Parts of lobules are constantly present. The cells of the tumor resemble closely liver cells, being, however, of a somewhat smaller size. Their cytoplasm stained in blue is finely granular and their nuclei are round or slightly irregular, containing a nucleolus, rich in chromatin. The cells are arranged in tubules and in strands. The tubules are of a small size and each consists of one row of cells (Fig. 5). In most of them, a lumen is present containing a drop of bile (Fig. 6). The columns of tumor cells are mostly present at the periphery of the tumor nodules, and in few areas they are in a continuity with normal liver trabeculae. This is conspicuous even under the low power where the difference in color of the cells is remarkable. Under the high power and especially with the oil immersion, the continuation of the liver cells into tumor cells is beyond any doubt. The tumor cells in these areas do not differ

markedly in size from the normal liver cells, the continuation of which they are. The difference is rather confined to the nuclei

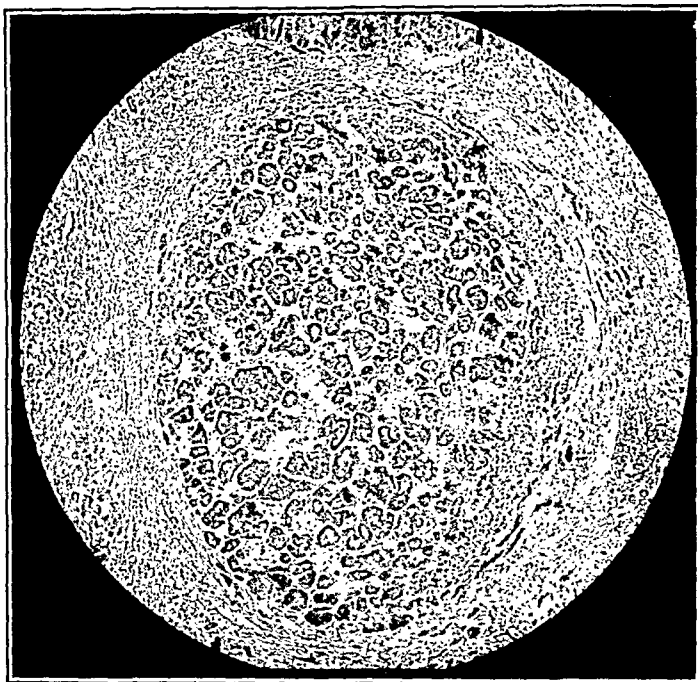


FIG. 5.—Case V. Hepatoma. A tumor nodule. $\times 70$.

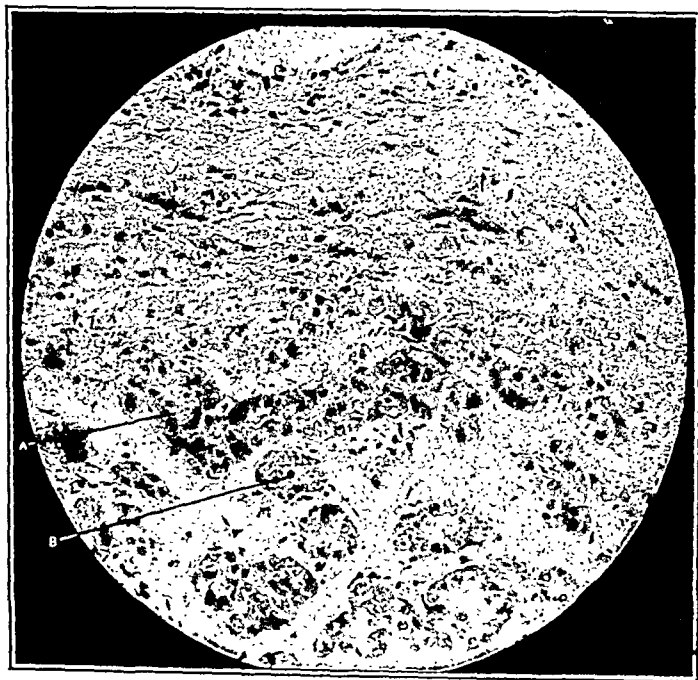


FIG. 6.—Case V. Hepatoma. A, continuation of normal liver cells into tumor cells; B, a drop of bile in the lumen of a tumor acinus. $\times 300$.

which are larger and richer in chromatin. The cytoplasm is stained with basic stains instead of the usual acid (Fig. 6). Mitotic figures could not be found in the sections.

Vessels: The vessels are largely invaded by tumor (Fig. 4). The portal veins in some areas are markedly distended, in others are of normal size and plugged with tumor. This is conspicuous not only in places where the tumor dominates the picture, but also in tissue very slightly touched by new growth.

Stroma: The stroma of the tumor consists of fine capillaries and closely resembles liver stroma (Fig. 7). No connective tissue is found between the tumor cells and group of cells.

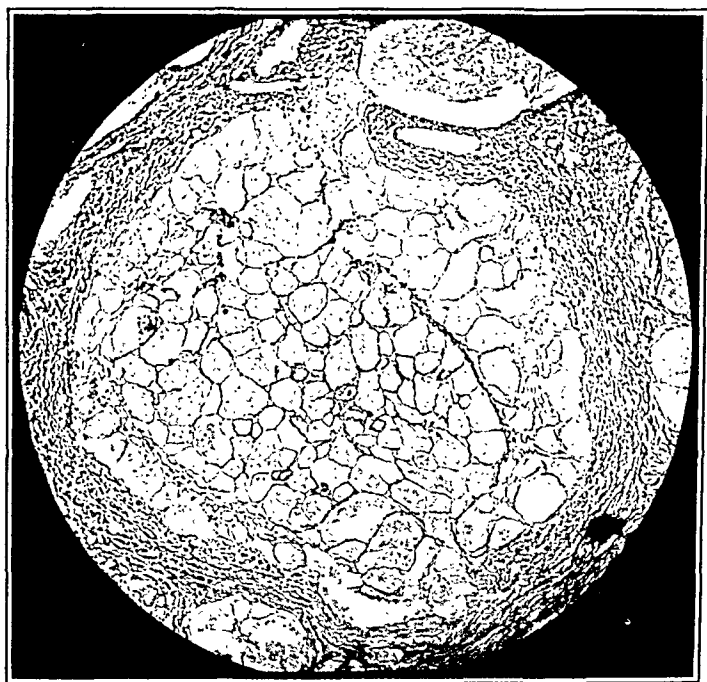


FIG. 7.—Case V. Hepatoma. The capillary stroma of the tumor. \times circa 55.

Lung Metastases: The tumor cells here are strikingly similar to those of the liver in their size, shape and staining properties. *These cells also secrete bile.* They are arranged in acini and irregular cords of columns with intervening sinusoids, so typical of the liver structure (Fig. 8). The tumor nodules are sharply demarcated from the lung tissue, the alveoli of which in the adjacent parts are collapsed and in the remote areas normal. Tumor tissue is found in the pulmonary vessels and in the perivascular lymphatics which are dilated. The stroma of the tumor here is also similar to the tumor stroma of the liver, being composed only of capillaries.

Spleen: Weighs 280 gm. and shows passive congestion.

Pancreas: Normal.

Kidneys: Arteriosclerotic changes in the vessels.

Adrenals: Normal.

Aorta: Atheromatous changes of the ordinary type.

Microscopical Diagnosis. Primary carcinoma (hepatoma) of the liver with metastases to the lungs. Tumor thrombi in portal and hepatic veins. Cirrhosis (portal) of the liver. Cholelithiasis. Ascites. Icterus. Chronic pleuritis (right). Arteriosclerosis; hypertrophy of prostate.

Discussion. As can be seen from the descriptions, the first 4 cases have in common:

1. The type of cells which closely resemble those of the smaller bile ducts, cuboidal or cylindrical cells with a narrow or large cytoplasm, a large vesicular nucleus and a deeply stained nucleolus.

2. The duct-like arrangement.

3. The connective-tissue stroma.

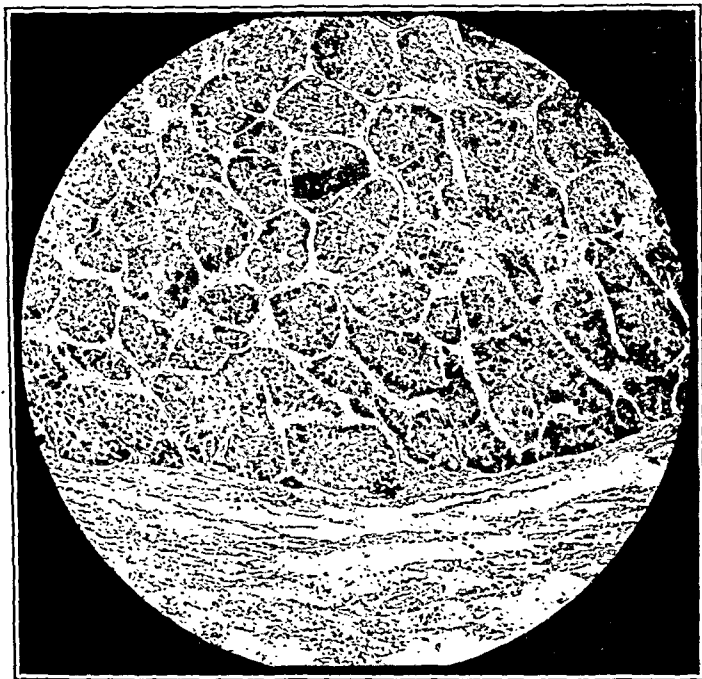


FIG. 8.—Case V. Hepatoma. Metastatic tumor in the lungs. $\times 70$.

In the fifth case the tumor cells are polygonal with a large, granular cytoplasm, containing a deeply stained nucleus. The cells resemble closely liver cells, not only morphologically, but also by their property, in the main tumor as well as in the lung metastases, of forming bile. The stroma in the tumor is also similar to the stroma of normal liver.

At one time there was a good deal of discussion as to whether the type of tumor was a hepatoma or a cholangioma, and the criteria for the differentiation between the two were based on the property of imitation of the structure of the tissues from which

they arose and the resemblance of the tumor cells to the matrix type cells.

However, cases were reported in which benign liver-cell adenoma had given rise to a duct-like structure (Orth quoted by Goldzieher and Bokay). It was also shown that the cells of the two varieties of tumor (hepatoma and cholangioma) may closely resemble each other. According to Ewing,¹¹ "Some cases are so far removed from their usual morphology that some doubt must always remain regarding their true origin."

Wegelin¹⁴ and Yamagiwa⁷ reached the conclusion that the stroma is a reliable criterion in the differentiation between the two types of tumor.

In hepatoma, the stroma consists of capillaries par excellence, while that of cholangioma is never composed only of capillaries.

The relation of liver cells to the capillaries, says Yamagiwa, quoted by Winternitz, is a property preserved by the tumor for the longest time, and apparently the tumor has the power to stimulate the endothelium of the vessels in which they lodge, to the formation of new capillaries of the liver nodule.

By using Pedrou's modification of Bielchowsky's silver-nitrate method we were able to demonstrate the striking similarity of the stroma in the normal liver tissue to those of the tumor in the liver and in the lungs (Fig. 7).

Thus, the resemblance of the cells of the tumor to the matrix type cell, the property to imitate the structure of the tissue from which they arise, and finally the stroma leads us to classify Cases I, II, III and IV as bile-duct carcinoma or cholangiomas, and the fifth case as a liver cell carcinoma or hepatoma.

Cirrhosis and Primary Carcinoma of the Liver. The strikingly frequent coincidence of cirrhosis with primary carcinoma of the liver, a coincidence which is unusual when the liver is the seat of a metastatic carcinoma, has impressed observers with the probable etiological relation between the two conditions.

The following tables taken from Winternitz, to which I have added statistics given by other observers, illustrate the percentage of the coincidence of primary carcinoma with cirrhosis.

HEPATOMA.

	Number of cases.	Percentage with cirrhosis.	Percentage without cirrhosis.
Eggel.	60	86.4	13.60
Goldzieher and Bokay	14	100.0	0.00
Yamagiwa	27	74.75	25.25
Karsner ¹²	4	100.0	0.00
Winternitz	6	100.0	0.00
Pirie ¹³	28	100.0	0.00

CHOLANGIOMA.

Eggel	8	62.5	37.50
Goldzieher and Bokay	7	42.8	57.20
Yamagina	15	46.7	53.30

The combined statistics, however, demonstrate that hepatoma is associated with cirrhosis in about 87 per cent of cases, and cholangioma is about 51 per cent.

Wegelin¹⁴ advanced the conception that cirrhosis follows cancer, explaining that as a result of the new growth, the liver parenchyma undergoes atrophy and necrosis, thus giving rise to the formation of scar tissue. However, the opinions that carcinoma follows cirrhosis is prevalent among pathologists.

Cirrhosis is explained as a repair process, due to injury followed by a compensatory hypertrophy and hyperplasia of the liver cells giving rise to the formation of multiple adenomatous nodules which may eventually become excessive to such a degree as to form carcinomata.

In a recent study on the incidence of hepatic carcinoma in the natives of Africa, Pirie¹⁵ found that primary carcinoma of the liver is much more frequent among natives than among Europeans. Thus in 96 cases diagnosed as carcinoma during a period of nine years (1912-1921) 36 were found to be primary in the liver. Twenty-eight of the 36 were liver-cell carcinoma, 3 bile duct, and 5 of a doubtful or mixed origin. *Cirrhosis was present in all of the 28 liver-cell carcinoma.* In searching for an explanation of the striking frequency of primary liver carcinoma and its association with cirrhosis in the natives, Pirie believed the cause to be schistosomiasis. The presence of the latter was definitely established by the author in 10 of the 36 cases, while in 24 information was lacking and only in 2 cases could it be excluded.

Schistosomiasis, as pointed out by Pirie, has been shown experimentally to induce cirrhosis of the liver. Fairley produced experimentally a bilharzial (*S. hematobium*) cirrhosis in monkeys. It is rather of interest to note that he believes the cirrhosis to be due not to the presence of the ova alone, which are present in a very scant number in the liver, but also to the bilharzial toxin present in the blood stream and which is filtered out in the liver. Fisher regards the deposit of the eggs of *S. japonicum* as the cause of the majority of the cases of cirrhosis of the liver in China. Symmers described a gross form of cirrhosis, "pipe-stem" cirrhosis, associated with the deposit of large numbers of bilharzial ova in the liver. (All the above mentioned authors are quoted by Pirie.) As a result, Pirie concludes: "Schistosomiasis may be a factor in accounting for the common occurrence of carcinoma of the liver among South African natives, through leading first to the development of cirrhosis on top of which a carcinoma may develop."

In the cases I, II, III and IV (cholangiomas) here reported, we believe the fibrosis to be secondary to the tumor, while in case VI (hepatoma) the tumor undoubtedly occurred on top of a previously existing portal cirrhosis.

Is the Tumor Multicentric or Unicentric in Origin? The multi-

centric origin of carcinoma of the skin, stomach and intestines was reported by different authors (Krompecher,¹⁵ Peterson,¹⁶ Versé,¹⁷ Hauser,¹⁸ Ménétrier,¹⁹ and others).

Recently, Dr. Margaret Warwick,²⁰ at a meeting of the Association of Pathologists and Bacteriologists in Boston, in an interesting demonstration, produced evidence of the multicentric origin of squamous cell carcinoma of the lower lip.

Siegenback van Heukelom,²¹ was the first to advocate the multicentric origin of primary carcinoma of the liver, basing his opinion on the observation of the transformation at the periphery of the tumor nodule of normal liver cells into cancer cells. He describes, for instance, columns of tumor cells as the continuation of normal liver cells and tumor capillaries in direct continuation with normal liver capillaries.

Goldzieher and Bokay⁶ also describe such transformation in some of their cases (10, 15 and 20) and believe in multicentricity.

Adelheim,²² in a study of 1 case of hepatoma without metastases to the lung or other organs, following nodular cirrhosis, demonstrates the "transformation" and convincingly advocates the multicentric origin of the tumor in his case.

Yamagiwa,⁷ on the ground that primary carcinoma of liver arises either as a regenerating hyperplasia of liver cells or as inflammatory hyperplasia of bile ducts, emphasizes the probability of multicentricity of every primary cancer of the liver.

The idea of appositional growth is energetically denied by Ribbert,⁵ who affirms that "Der völlig entwickelte Krebs wächst immer nur aus sich heraus" and by Borst (quoted by Ménétrier) who affirms that "the carcinoma on the border advances with its own troops and does not add to itself new soldiers at the expense of healthy tissue."

The fact that tumor thrombi are found practically always in the liver vessels indicates once more, according to Ribbert, that the tumor spreads by the way of metastases to other organs and to other points in the liver itself.

Winternitz,⁹ who is also against multicentricity, emphasizes the presence of tumor masses in the vessels of the portal areas.

Helvestine²³ reported 1 case of hepatoma *without cirrhosis* in which the cancer cells grew between parallel capillaries and were in direct continuation with the liver cells trabeculae, but there was no transition between liver cells and tumor cells. He compared the case with a metastatic carcinoma from the gall-bladder and found appearances very similar to those found in the hepatoma, and as a result he concludes the growth to be unicentric.

To trace the multicentric origin in cholangioma is not always possible, because of the fact that the cases come to autopsy when the liver is markedly involved by the new growth and the large tumor

mass present might well be due to the confluence of several small nodules which had started at different points at the same time.

However, as has been pointed out in the description in cases I, II, and IV the tumor appears to be confined mostly to the portal areas from which it extends for some distance. Even beyond this extension, there is a marked proliferation of the bile ducts the cells of which, in places, are taller than normal and form papillary projections into the lumen. In Case II they rupture the basement membrane and invade the surrounding tissue.

These facts, in connection with the opinion expressed by Yamagiwa, that the tumor is due to an inflammatory hyperplasia of the bile ducts, are suggestive that the growth is multicentric.

As regards the hepatoma, two facts dominate the picture:

1. The strikingly diffuse and practically *uniform* distribution of the tumor corresponding to the involvement of the liver by the cirrhotic process, which suggests that the tumor started at different points at the same time.

2. The relative scantiness of tumor metastases in the lungs and the absence of metastases in other organs as compared with the extreme invasion of the vessels, rather plugging them by the new growth.

This "invasion" upon which so much stress has been laid to prove the unicentric (metastatic) theory, I believe (in the case reported here) to be due to a passive discharge of tumor mass into the vessels. This belief is strengthened by the fact that the tumor in the vessels is found to be largely necrotic. Dr. Wolbach (personal communication) observed a case where the tumor thrombus extended into the vena cava up to the heart.

The presence of tumor metastases in the lungs, however scant they are, obviously shows that the tumor spreads by metastases also.

Correlating the facts just mentioned with the "transitions" described by Heukelom, Goldzieher and Bokay and others and also found by myself in many areas in Case V, I am inclined toward the conception that the growth spreads in unicentric as well as multicentric manner believing that in hepatoma the latter is the principal way in the spread of the new growth.

Clinical. The first writers on the subject believed they were able to diagnose not only the disease but even the type of cancer (nodulary, massive and so forth). In time, however, this belief was disproved, and from the records reported in the literature, the diagnosis of primary carcinoma of the liver was rarely made ante-mortem. In most instances the clinical picture points rather to a cirrhosis or to any liver disturbance producing portal obstruction. Jaundice, edema of the lower extremities, ascites, weakness and loss of weight are the leitmotif of the patient's complaint.

The involvement of the lungs is, of course, not as rare as it is commonly taught, and occurs probably early. There are, however, few signs on physical examination, as is seen in Case II, where in spite of extensive metastases to both lungs the attention of the clinician was drawn to the *extensive* involvement of the lungs by the low vital capacity which was about 41 per cent of normal.

The difficulty in diagnosis is amply demonstrated by the fact that *in none of our cases* was the condition diagnosed antemortem.

AGE AND SEX. Primary carcinoma of the liver attacks people practically of the same age as carcinoma elsewhere, notably between the fourth and fifth decades. In our cases, the age varies between sixty-one and sixty-six years. However, many cases have been reported of primary carcinoma in children.

Hepatoma seems to be more frequent in males, while cholangioma in the female is prevalent. This may be explained by the predominance of cirrhosis of the liver in men, and bile-duct infection, followed by an inflammatory hyperplasia of bile ducts, in women.

COURSE. According to the literature, primary carcinoma of the liver runs a rapid course and is rarely of more than three months' duration.

In the cases here reported the exact onset of the disease was impossible to determine. The patient's attention to this condition is generally drawn two to three months before exitus.

Summary and Conclusions. Five cases of primary carcinoma of the liver are reported. Cases I to IV are classified in cholangiomas, or bile-duct carcinoma, and Case V is classified as hepatoma, or liver-cell carcinoma.

The differential diagnosis between the two varieties of tumor is based:

1. On the type of cells. In cholangioma, the cells resemble those of the smaller bile ducts; in hepatoma, the liver cells.

2. On the arrangement of the cells. In cholangioma they have an arrangement closely resembling bile ducts, while in hepatoma they are arranged in columns, imitating the normal liver structure.

3. On the type of stroma which is considered as the most reliable criterion. In cholangioma, the stroma is fibrous, while in hepatoma it consists of capillaries, strikingly resembling the normal liver stroma, not only in the liver tumor but also in the lung metastases. This is demonstrated by Pedrou's modification of Bielchowsky's silver-nitrate method.

In all 5 cases metastases are present in the lungs and in 1 case also in the kidney.

Tumor is found invading the liver vessels in all cases.

In the hepatoma (Case V) areas of transition between normal liver cells and tumor cells are present.

Both varieties of tumor are believed to spread by either way: multicentric and unicentric.

In hepatoma, the tumor has occurred on top of a cirrhosis, while in the cholangioma the fibrous stroma is secondary to the tumor.

The 4 cases of cholangioma here reported, happened all in women. The age of the patients varied between sixty-one and sixty-six years. The hepatoma happened in a man.

Ascites was present in 3 cholangiomas and also in the hepatoma.

The exact onset of the disease in the cases reported was impossible to determine, but the patients attention was drawn to this condition two to three months before exitus.

In no instance was the diagnosis of this condition made in the cases reported antemortem.

LITERATURE.

1. Kelsh and Kiener: Contribution à l'étude de l'adenome du foie, Arch. de. Physiol., 1876, 2, 3, 622.
2. Sabourin: Contribution à l'étude des lésions du parenchyme hepaticque dans la cirrhose, Essai sur l'adenome du foie, Thèse, Paris, 1881.
3. Hanot et Gilbert: Étude sur les maladies du foie, Paris, 1888.
4. Eggel: Ueber der Primare Karzinom der Leber, Ziegler's Beitr., 1901, 30, 506.
5. Ribbert: Das Karzinom des Menschen, Sein Bau, Sein Wachstum, Seine Entstehung, Bonn, 1911; Geschwulstlehre, Bonn, 1914; Deutsch. med. Wchnschr., 1909, 35, 1607.
6. Goldzieher and Bokay: Das primäre Leberkrebs, Virchows Arch., 1911, 203, 75.
7. Yamagiwa: Zur Kenntniss der primären parenchymatosen Leberkarzinom (Hepatoma), Virchows Arch., 1911, 206, 437.
8. Hansemann: Ueber das primären Krebs des Leber, Berl. klin. Wchnschr., 1890, 27, 353.
9. Winternitz: Primary Carcinoma of the Liver, Johns Hopkins Hosp. Repts., 1916, 17, 143.
10. Clawson and Cabot: Primary Carcinoma of the Liver, Jour. Am. Med. Assn., 1923, 80, 909.
11. Ewing: Neoplastic Diseases, 1919.
12. Karsner: A Clinico-pathological Study of Primary Carcinoma of the Liver, Arch. Int. Med., 1911, 8, 238.
13. Pirie: Hepatic Carcinoma in Natives of Africa and its Frequent Association with Schistosomiasis, Med. Jour. South Africa, 1921, 17, 87.
14. Wegelin: Ueber das Adenokarzinom und Adenom der Leber., Virchows Arch., 1905, 179, 95.
15. Krompecher: Der Basalzellenkrebs, Jena, 1903.
16. Peterson, W.: Beiträge zur Lehre von Carcinom, Beitr. z. klin. Chir., 1902, 32, 543.
17. Versé, Max: Ueber die Histogenese der Schleimhautcarcinome, Verhandl. der deutsch. path. Gesell., 1908, 12, 95.
18. Hauser, G.: Zur Histogenese der Krebse, Virchows Arch., 1894, 138, 482.
19. Ménétrier, P.: Cancer, Traité de Médecine et de Thérapeutique, Brouardel et Gilbert, Paris, 1908.
20. Warwick, Margaret: Communication at the meeting of the Association of Pathologists and Bacteriologists at Boston, March, 1923, and by personal communication.
21. Heukelom: Das Adenokarzinom der Leber mit Cirrhose, Ziegler's Beitr., 1894, 16, 241.
22. Adelheim: Frankfurt Ztschr. f. allg. Path., 1913, 14, 320.
23. Helvestine: Primary Carcinoma of Liver, Jour. Cancer Res., 1922, 7, 209.

THE SURGERY OF PULMONARY TUBERCULOSIS.*

BY JOHN ALEXANDER, M.A., B.S., M.D.,

ANN ARBOR, MICHIGAN.

(Continued from July, 1924)

CAVITIES whose walls are not very stiff are obliterated to mere clefts by successful thoracoplasty; these clefts then fill with granulation tissue rich in bloodvessels and become obliterated, or a smooth, clean mucous membrane replaces the previous dirty lining.

The uncompressed lung compensates for its compressed fellow by becoming huge with emphysema and hyperplasia.

Brauer does not think that in a resting patient any noteworthy greater functional demand is made upon the functioning lung, except perhaps during the period immediately following the operation, before it has accustomed itself to the sudden change in intrathoracic pressure conditions. Sauerbruch, on the other hand, states that the uncompressed lung, especially in the young, moves much more after operation, and that this causes a more rapid movement of lymph and, if it contains tubercle bacilli, dissemination of disease, and that the increased movement may be responsible for the breaking down of partially healed lesions. It is for these reasons that Sauerbruch lays such great stress upon the necessity of the better lung being absolutely free of tuberculous activity if the worse lung is to be permanently compressed by thoracoplasty.

IV. Thoracoplasty Compared with Artificial Pneumothorax. At present the working rule that thoracoplasty is never to be used when satisfactory artificial pneumothorax is obtainable is almost everywhere strictly observed. Inquiry into the differences between the methods, and the relation between them, will be of value for a better understanding of thoracoplasty.

The number of patients whose pulmonary disease is sufficiently unilateral to warrant compression of one lung is variously estimated at from 2 to 10 per cent. Matson *et al.* attempted artificial pneumothorax in 600 of 7000 patients, or 8.5 per cent; of these, 120 (20 per cent) had no free pleural space. In 248 (41.3 per cent) only partial compression was obtainable, and the clinical cures were only 15.5 per cent, whereas the satisfactory compressions produced 45 per cent of clinical cures. Saugmann has reported the results of attempted artificial pneumothorax upon 211 third-stage tuberculous patients: 70.2 per cent were able to do "ordinary light work" when the pneumothorax had been complete; 33.3 per cent when there were only limited adhesions; only 11.1 per cent when there were extensive adhesions, and 11.8 per cent when no pneumothorax at all was realizable. Saugmann estimated that he failed to produce satisfactory compression in 30 per cent of his attempts; von Muralt

gives 20 to 30 per cent as his figures; Brunner 50 per cent; Stuertz 20 per cent; Powell and Hartley 30 per cent. Thoracoplasty is not indicated, however, for all cases in which pneumothorax has failed (this will be discussed under indications and contraindications).

Madinier and Saugmann estimate that 4 to 8 per cent of their patients are suitable for surgical therapy. I believe that with conservative choice of cases, 2 per cent is nearer the true estimate for unselected groups of tuberculous patients.

Experience has taught that the only sure way of telling whether or not a pleural cavity is so far obliterated by adhesions as to prevent the production of an artificial pneumothorax is to try to find a free pleural space by repeated actual trials. In other words, the usual signs of adhesions are not sure clinical signs, as a much contracted chest may mean only an advanced pulmonary sclerosis with a free pleural cavity. However, a history of pleurisy, a sunken chest in a chronic ulcerative phthisis, diminished respiration and fremitus, and a negative Litten's sign, and an immobile diaphragm as determined by physical examination and roentgen-ray, are practically certain evidence of extensive pleural synthesis.

Numbers of series of cases show that the final results of pneumothorax and of thoracoplasty are about the same, that is, roughly, 35 per cent cured, 30 per cent improved, 35 per cent uninfluenced, worse or dead. Empirically, therefore, it cannot be claimed that thoracoplasty is less effective because it produces less compression than pneumothorax. Each method has certain advantages over the other that will be of interest to examine.

Pneumothorax, in contradistinction to thoracoplasty, is non-deforming, non-shocking, and as compression is produced gradually, at many sittings, it avoids the dangers of acute circulatory and respiratory upsets, and of pneumonia from aspiration of large amounts of expressed secretions, or failure to expectorate them on account of operative pain. Also, as accumulated toxins are only gradually squeezed out of the lung into the general circulation (auto-tuberculinization) there is little danger of lighting up tuberculous foci elsewhere in the body, and the operation of pneumothorax, *per se*, does not lower general resistance. Pneumothorax has the advantage that it may be rapidly released (provided it is not of long standing and the lung and pleura much fibrosed—for then attempted release only aggravates the dyspnea) in case pneumonia, pleurisy, severe bronchitis or progression of tuberculosis (7.3 per cent of Matson's 480 cases) develops in the opposite lung. Thoracoplasty once done is beyond recall, and the complications just named are liable to be fatal.

Although thoracoplasty upon tuberculous persons is distinctly a major operation with a definite operative mortality (2 to 10 per cent), the new technic, and especially operation in several stages, has made it remarkably safe. While the operation of artificial

pneumothorax is an essentially trivial procedure, it entails many grave risks. Gas embolus and "pleural eclampsia" are real dangers, although not always fatal. Forlanini had 4 such "accidents" among 1454 gas fills (0.27 per cent), or 14.28 per cent of the patients under treatment. Matson *et al.* had two fatal cases (0.33 per cent) of gas embolus; 2 fatal, and 15 non-fatal cases of "pleural eclampsia."

It is generally estimated that 50 per cent of all pneumothoraces develop serous effusions during the course of treatment. In many of these, fibrinous adhesions form under the fluid and slowly but certainly draw the lung out to the chest wall where it adheres tightly and obstinately refuses further gas compression. McKinnie estimates that 5 per cent of these effusions become purulent, a grave complication, especially if the pus becomes secondarily infected. Of Matson's 480 cases 12.3 per cent developed purulent effusions. When the pyo-pneumothorax occurs suddenly from a large rupture of the lung or of a superficial, thin-walled cavity (usually as the result of trying to stretch adhesions with high positive gas pressure) the outcome is most frequently early death. Of Sauerbruch's 73 cases of cavity rupture, 57 were caused by such attempts to stretch adhesions; of these 57, 43 died during the first week, 6 in later weeks, a total mortality of 86 per cent. Of his 16 spontaneous pneumothoraces only 4 died (25 per cent). Spontaneous pneumothorax occurred in 3.3 per cent of Matson's series.

It is common knowledge that the immediate results of pneumothorax are frequently so satisfactory to some patients that they fail to return for the necessary continuation of the treatment. Fishberg believes that most poor people abandon pneumothorax refills after leaving the sanatoria, and on this account advises the treatment only for the well-to-do who can, and will, continue. Once the gas has absorbed and the lung expanded, firm pleural adhesions form, and almost invariably prevent resumption of pneumothorax therapy when the wayward patients return for it because of the return of active symptoms; then thoracoplasty must be resorted to. Ten (2.08 per cent) of Matson's 480 patients abandoned treatment too soon because they were doing so well. According to the case, it is necessary to inject gas every two to three weeks for from one and a half to three or more years. In 1923 Gravensen, Saugmann's successor, wrote that he "usually maintains an optimal pneumothorax three to five years." There are many who loathe the prospect of being the object of even so minor an operation over a period of years. A thoracoplasty once done is done; and for this reason may be considered especially indicated for those poor or shiftless persons who might be expected to abandon pneumothorax treatment prematurely. As the improvement after the first stage of the operation is rarely so marked as to lead the patient to believe that he is cured, he almost invariably accepts the second and final stage. In regard to its permanency, thoracoplasty possesses a far

more important advantage than this. In a typical case, after a long period of pneumothorax treatment, during which all the symptoms of tuberculosis have disappeared, the physician in charge decides to stop the gas injections and to allow the pneumothorax to absorb. This has been aptly described as "a jump into the dark," as it is always impossible to predict when tuberculosis is permanently healed. Arrest of the disease has been effected by pulmonary rest, and the encapsulation of tubercles and cavities with fibrous tissue, which by shrinking has made the lung relatively smaller than its containing chest wall. As such a lung expands, the encapsulating fibrous tissue is tugged at, and unless very firm it will be torn apart and the tubercles it contains exposed and activated, and cavities pulled open. This reactivation of the tuberculosis is not infrequently observed clinically, but often after pleural adhesions have formed, preventing resumption of gas compression; in such cases thoracoplasty becomes necessary. As the lung expands, it resumes respiratory movements—a further stimulus to reactivation of the disease. It is sometimes claimed that one of the most important advantages of pneumothorax over thoracoplasty is that after release of the gas the lung resumes its normal function instead of being forever useless. As a matter of fact, if the compressed lung was extensively diseased before the institution of the pneumothorax, it will become so filled with scar tissue after one or two years of treatment that it is of little use in respiration after it has expanded.

As the chest cavity is larger than the greatly shrunken lung that is expected to fill it, various changes occur in an attempt to compensate for the discrepancy: the hemithorax flattens and the ribs crowd together, and the heart and mediastinum and diaphragm shift toward the affected side and the relatively normal portions of both lungs become emphysematous. If these changes do not suffice, the intrapleural negative pressure becomes very great as the gas is absorbed, pain and dyspnea may be marked, and "*transudates ex vacuo*" appear. After many months these transudates may become purulent and require eventual thoracoplasty.

Within the past two or three years several clinics have been using phrenicotomy in conjunction with pneumothorax; the marked rise of the diaphragm has been found largely to compensate for the disproportion between the chest and contracted lung. This will be discussed further under the section, paralysis of diaphragm.

There are certain cases in which thoracoplasty would be chosen in preference to pneumothorax. It is preferable to the operation of intrapleural pneumolysis, or the use of Jacobaeus' thoracoscope and cautery for adhesions (except when they are few, long and slender) that are preventing a completely satisfactory gas compression. The combination of either of these operations with artificial pneumothorax exposes the patient to the dangers and later complications of two distinct operative procedures. Thoracoplasty is

also preferable to attempts to stretch or tear adhesions, which may be near superficial lesions or cavities, with high gas pressures, because of the danger of lung rupture and rapidly fatal empyema (Blanchette; Olbrecht; Sauerbruch—see his statistics above). Sometimes a gas compression will be satisfactory except for one adhesion located over a cavity, and which may pull in such a way as to cause hemorrhage. Such cases need thoracoplasty. There are certain stiff-walled cavities that thoracoplasty will collapse after pneumothorax has failed (Brauer; Leon Bérard).

Some surgeons with wide experience with both methods believe that thoracoplasty is preferable to pneumothorax, although few are as yet sufficiently firm in their belief to expose their patients to the dangers of a major operation, if satisfactory compression is obtainable with pneumothorax. Sauerbruch considers thoracoplasty more "bedeutungsvoll" than artificial pneumothorax, and says that many doctors, who are in the position to compare the results of the two methods, "recognize the better and lasting results of extensive rib resection." On the basis of a comparison of Jehn's 6 necropsies upon old thoracoplasty patients with necropsies upon pneumothorax patients, Sauerbruch says that the fibrous tissue is greater in amount after thoracoplasty than after pneumothorax.

Hauke points out the fact, which he admits may be more of theoretical than practical importance, that as the air of a pneumothorax is always absorbing the lung is continuously expanding, whereas after thoracoplasty the "deribbed" chest wall falls in, in proportion to the amount of pulmonary fibrosis, until rib regeneration finally fixes it. Bérard and Dumarest believe that pneumothorax bulges the mediastinum farther toward the better lung than does thoracoplasty, and, in demanding more strenuous work of it, exposes any latent lesions that it may contain to greater danger of activation. Jessen believes that thoracoplasty is indicated for all very severe lesions, because the lasting results are better, and says, "the results from thoracoplasty, if the indications are properly placed, are reached by no other method." When compression therapy is indicated, Trembley, an internist, would advise thoracoplasty in preference to pneumothorax (because of the many dangers, complications and uncertainties of release of the latter) if two-thirds of a lung were considerably diseased. Bérard and Dumarest use thoracoplasty (partial) in the presence of a free pleural cavity for localized, ulcerative infiltration or cavity of the base, and Moreau and Olbrechts would prefer a complete thoracoplasty for pneumonic types of infiltration which are little influenced by artificial pneumothorax. Stöcklin, an internist, thinks that better care in selecting cases and better technic will make thoracoplasty results surpass those of artificial pneumothorax, and adds, "it is, indeed, to be expected that in the future thoracoplasty will prove superior to pneumothorax."

V. Indications and Contraindications. Only through active coöperation between internist and surgeon is it possible to select cases rationally and to avoid great disappointments. In brief, surgical compression may be said to be indicated for largely unilateral lesions, when all other treatment, including a sufficiently long sanatorium régime and attempted artificial pneumothorax, has failed.

At present few internists will recommend operation until the patient has "cured" for many months and has steadily "lost ground," and for whom death seems a certainty. Operation is usually thought of only as a last refuge, and that it has been able to accomplish so much even in such cases is promise that it may be expected to accomplish much more when broader experience more clearly defines the exact indications and contraindications, and when patients are referred for surgery before the disease has become far advanced with cavity formation and, perhaps, repeated hemoptyses. Davies advises operation if there has been no improvement after six months of faithful sanatorium régime, but would operate at once if cavity exists. From many experienced surgeons and internists comes the plea for earlier operation, especially for patients with incomplete artificial pneumothoraces who are not making satisfactory improvement.

Contrary to expectation it has been found that even very sick tuberculous persons, with high fever, cavities and much sputum, stand these major operations remarkably well. However, both Sauerbruch and Schottmüller point out the danger of operating upon those who have demonstrated an abnormally poor resistance to tuberculosis, or whose family tuberculous history is markedly bad.

Age. In general the operation should be limited to patients between fifteen and forty-five years of age. However, apparent age, and the condition of the cardiovascular system are more important than actual age. Sauerbruch does not hesitate to perform the two-stage operation upon a person over fifty if the general condition is satisfactory, nor upon a child under fifteen, if lung compression is absolutely indicated. In children the bony tissues are so plastic that only very small resections are needed to obtain considerable compression. Jacobaeus and Key had definitely bad results among patients under twenty, and say this is also the experience of other surgeons. Brauer states that the indications for operation are the same in children as in adults, but that it should be advised for the young only with the greatest caution; the common caseous, hepaticized forms, with hilus foci, not uncommon in children, are to be avoided. It is still too soon to know if the favorable results thus far obtained will outlast puberty. As there are not often many adhesions in children, pneumothorax is usually possible (Brauer); Eliasberg has reported good results with it in parenchymatous lesions, and says that without it children are sure to die.

The Worse Lung. Very extensive diseases of even three lobes of one lung is no contraindication, provided that the patient's general condition is satisfactory. A great majority of the reported cases had cavities, and the most startling immediate results have occurred in them. Operation is especially indicated where basal lesions are marked, as spontaneous healing is rare on account of the great range of respiratory movements (Saugmann; Madinier). Better results are obtained from operation upon the left lung than upon the right; this is said to be due to the facts that the compression of the left side is relatively greater because the left lung is smaller, and that relatively less work is thrown upon the right lung, it being larger. Of Schottmüller's 100 cases, 57 were operated upon the left side: there were 40.4 per cent final cures and 17.5 per cent final deaths; 43 were on the right: 32.5 per cent cures and 32.5 per cent deaths. Of Sauerbruch's last 116 operations 63 were left-sided: 52 per cent lost tubercle bacilli, 24 per cent improved, 10 per cent remained unchanged, and 14 per cent died; 53 were on the right: 20 per cent lost tubercle bacilli, 30 per cent improved, 12 per cent remained unchanged, and 36 per cent died. Of Bull's 75 operations, 46 were left-sided, and there were 2.2 per cent operative deaths; 29 were on the right side, with 26 per cent operative deaths. Of Jacobaeus and Key's "positive results" 18 were on the left side, 6 on the right; of their "negative results" 11 were on the left side, 7 on the right.

In regard to lung pathology it is of the greatest prognostic importance that the lesions be predominately chronic and fibrous, or "productive" in type, rather than rapidly progressive, caseous, or "exudative" in type, for these last do not respond so favorably to compression. Productive lesions are distinguishable by roentgen-ray and physical examination: the individual lesions are dense and compact, the chest is contracted, the heart, mediastinum and trachea pulled over and the diaphragm up, and the ribs are inclined markedly downward and are close together. The lesions among Sauerbruch's last reported 116 cases were predominately productive in 67, and months or years after operation there were only 10 per cent of deaths; among 49 predominantly exudative cases there were 43 per cent deaths. Progressive, exudative lesions in the worse lung usually imply progressive tuberculous activity in the better, and the results, therefore, are frequently bad. Patients with such lesions may be operated upon only as a last resort, and only then when their general condition is good, and when the "good lung" is free of even small "spots." Jacobaeus and Key had 7 unfavorable results from operation upon 7 patients whose tuberculous history dated back less than one year.

Sauerbruch does not consider great amounts of sputum a contraindication, provided the patient is an otherwise suitable case. He

has operated where there were 1000 cc a day, which became reduced to 1 or 2 cc a day.

Some form of surgical compression is indicated for recurrent severe hemoptyses when artificial pneumothorax cannot be produced, or where adhesions, in the presence of a partial pneumothorax, tug upon lung tissue over a bleeding vessel and prevent its closing. Sauerbruch rarely operates for a first severe hemorrhage. Pribram advises trying the minor phrenicotomy before using more severe measures. Stöcklin advises pneumolysis with paraffin "fill," in preference to a thoracoplasty, as: (1) it is a less severe operation; (2) there is less chance of suffocation if another large hemorrhage occurs and the mechanical conditions for expectoration are better; (3) greater pressure can be exerted upon the bleeding vessel, if the mediastinum is well fixed. Sauerbruch does his typical paravertebral thoracoplasty if the hemorrhages have been small and the patient is in good condition, but if not, he resects portions of only ribs I, II and III paravertebrally, then strips the pleura from the ribs and packs with a gauze tampon. Forty-two of Stöcklin's 100 thoracoplasties had had hemoptysis prior to operation, but he never saw it recur during operation, although 4 patients bled from upper lobe cavities several days after first stage operation, when the lower ribs were resected, developed aspiration pneumonia in the better lung and 2 of them died.

The So-called "Good" or Better Lung. Inability to foretell accurately whether or not the disease that exists in the so-called "good lung" will progress after operation is the chief hindrance to an accurate selection of cases for operation. Among the 824 patients of my collected series who were judiciously selected for operation and managed in accordance with the best known methods, only 143 (17 per cent) died after the first postoperative month, whereas 55 (27.5 per cent) of the 200 patients, who were not so carefully selected and managed, died after the first postoperative month. Bull calls the "good" lung "the sword of Damocles." Brauer finds that from 10 to 15 per cent of those who have been operated upon show progression of the lesions in the better lung, usually to death. This progression may be accounted for by; (1) the increased work the better lung is called upon to do after the other lung is shut out from function; (2) the normal tendency of much tuberculous disease toward progression; (3) activation by massive "auto-tuberculinization," the result of sudden squeezing out of toxins from the worse lung at operation. Pathologically it is a great rarity to find any considerable disease in one lung and literally none in the other, although strictly unilateral disease may be not infrequent clinically. In general, most clinicians of experience are agreed that if tuberculosis is demonstrable by roentgen-ray or physical examination in the better lung, it must be only of small extent and limited to the

apex, and non-progressive during an observation period of several months. Sauerbruch, Brauer, Bull and Stöcklin, Bérard and Dumarest, men of the widest experience, say that any lesions in the better lung must be absolutely inactive, that is, quiescent or arrested. Jacobaeus and Key state that the size of the lesions is of less importance than the degree of their activity, and that old shrunk lesions offer the best prognosis. Lorey says that the better lung must be "practically sound." Sauerbruch believes that the clinical signs are of greater importance than the roentgen-ray in judging clinical activity in the better lung, and, of course, urges a careful combination of the two methods; if in doubt he advises prolonged observation in a sanatorium; Jacobaeus and Key say for six months; Archibald advises six to twelve months sanatorium observation of the better lung before performing the second stage, if it has shown suspicious signs after the first stage. Sauerbruch has proposed a preliminary phrenicotomy on the worse side in cases of doubt as to tuberculous activity of the better. This throws a small amount of extra work upon the better lung, and lesions with tendency toward activity are very apt to light up temporarily and thus warn against performance of the major operation. If they remained unchanged for two to three weeks thoracoplasty may be undertaken (Fischer). Sauerbruch and others have found this functional test of great value, and it has the further advantage of causing some improvement and rest of the worse side, thereby putting the patient in better condition for a thoracoplasty, if found indicated.

If apprehension is felt about permanently throwing upon the better lung even the slightly increased work that contralateral phrenicotomy does, use may be made of a procedure that Fischer practises as a test of the better lung before performing definitive phrenicotomy. The accessory phrenic nerve is partially resected and a 1 mm. wide tube of ice (Perthes) held against a 2 to 3 mm. length of the main phrenic stem for fifteen seconds. This produces only temporary diaphragmatic paralysis, and if the lesions in the better lung do not become activated within the next three weeks permanent phrenicotomy and thoracoplasty, or thoracoplasty alone may be done. From experiments upon rabbits Balderry found that if the phrenic stem is sprayed with ethyl chloride for ninety seconds (which frosts the nerve for forty-five seconds) there follows an immediate diminution in diaphragmatic motion, which becomes more marked at ten hours; electric stimulation of the nerve ten to fourteen days after the freezing causes no diaphragmatic contraction, but within five to seven weeks motion returns.

As the validity of the better lung is of great importance to the economy after the other lung has been permanently prevented from functioning, it must be sound in all respects—without bronchitis, bronchiectasis, asthma, pleural pain or extensive adhesions that might restrict respiration.

There is a rapidly increasing tendency to use pneumothorax upon patients whose better lung shows definite tuberculous activity of the upper lobe, upon the theory that by eliminating the grossly diseased, worse lung as the main source of toxin formation, the lesser lesions are enabled to use the whole of the body's resistance for recovery. This action is comparable to the improvement of pulmonary lesions after the resection of a tuberculous joint, and of the better of two kidneys after the removal of the worse. Of Matson's 480 artificial pneumothoraces 282 had demonstrable disease on the better side, and yet, during treatment, progression occurred in only 35 of them (12.4 per cent). As the principle is the same for surgical as for gas compression, except that the physiological changes are produced more abruptly, there is a definite tendency among many surgeons to be more lenient as to demanding absolute inactivity in the better lung as a prerequisite for operation. Eloesser says that the better lung need not be absolutely sound—"no large cavity or evident active area" that would be apt to light up. Davies and Jessen say that the lesions must not be extensive or acutely active. Saugmann operated in the presence of some "badness," and in all of his 40 cases there was some, as in all of Archibald's first 15. If there is more than a little active disease on the good side, and if thoracoplasty is the only hope, Brauer and Gravensen would operate if there were no other definite contraindication; some improvement may be expected. Both Saugmann and Sauerbruch have obtained improvement when the better side was considerably involved at the time of operation, but warn that pleasant surprises are far less frequent than unpleasant ones. Sauerbruch pleads against the operation *ut aliquid fiat*; in the final stages of consumption patients and their families are inclined to beg for any last chance, but operation in the presence of definite contraindications only makes death worse because of suffocation from insufficient lung ventilation, and pain. As a rule Sauerbruch will operate in the presence of activity in the better lung only when the worse lung has been almost entirely destroyed, and where the respiration in the better lung has compensated.

The smallest active lesion in either the hilus or lower lobe of the better lung absolutely contraindicates operation for Sauerbruch and Stöcklin. Brauer will not operate if there is "a small lesion at the base or a larger one at the hilus," nor will Bull if there is any lesion at all, old or recent, at the base. On the other hand, Jacobaeus and Key do not hesitate to operate if small lesions at the "good" hilus or base are relatively inactive; they have operated upon 9 patients with roentgen-ray or auscultatory evidence of tuberculosis in the lower half of the "good" lung, and 7 of them were improved.

Next in importance in deciding for or against operation is the condition of the cardiovascular system. One-half of Stöcklin's

operative deaths occurred from heart failure, and now he refuses to operate if he is in doubt as to the soundness of the heart. Even compensated valvular lesions are contraindications for Madinier. The lung fibrosis in tuberculosis does tax the right heart to some extent, and the operative compression of the lung makes further demands upon it. Careful functional tests of the cardiovascular system are essential for sound judgment of a patient's suitability for operation.

Sauerbruch, Brauer and Bull have called attention to those cases of cardiac distress and dyspnea due to extreme displacement of the heart and trachea toward the side of an adherent, shrunken lung, and to the great relief afforded by an ordinary thoracoplasty, which acts in the manner of a cardiolysis. When its effect is insufficient Sauerbruch performs a classical cardiolysis, removing the periosteum with the ribs.

Bones and Joints. Bull considers thoracoplasty contraindicated in the presence of any bone or joint tuberculosis; von Muralt in the presence of Pott's disease. Stöcklin says that a single bone lesion should not contraindicate.

Insanity. Sauerbruch warns against psychotic tendencies, as they might develop postoperatively and cause the patient to tear open his wound, to insist on exercising, or to refuse to expectorate. However, curable psychoses do not necessarily contraindicate operation.

Pregnancy. Artificial pneumothorax has been initiated during pregnancy, with satisfactory results. If adhesions should prevent the use of pneumothorax, a therapeutic abortion should take precedence over thoracoplasty.

Larynx. There is general agreement that mild and midsevere laryngeal tuberculosis almost always improves after thoracoplasty. Brauer says that deep disease is a contraindication, but Saugmann said that acute progressive disease is not a definite contraindication, as without operation such patients are certain to die.

Kidney. Any organic nephritis, including amyloid degeneration, contraindicates thoracoplasty (Brauer; Stöcklin); von Muralt said that mild amyloid is favorably influenced. Any renal tuberculosis contraindicates, according to Brauer and Bull, although Stöcklin states that unilateral renal tuberculosis does not contraindicate, and Jessen says that it merely decreases the chances of clinical success. The milder grades of diabetes do not contraindicate, but the severer ones absolutely do.

Intestines. Every continental author absolutely condemns operation when there is the least tuberculous involvement of the intestines, with the possible exception of ischiorectal disease. Matson *et al.* say it does not contraindicate pneumothorax therapy if it is not so severe as to interfere with proper nutrition. As a

result of the rapid strides being made in the treatment of intestinal tuberculosis with heliotherapy, it may be that minimal intestinal involvement will soon be considered not to be a definite contra-indication.

VI. Choice of Operation. Many variables as to type and location of lesions and as to the general clinical condition of the patient, combine to make it obviously impossible to present any hard-and-fast rules as to choice of operative technic.

It may be said that, in general, most cases for whom operation is indicated will do best after a two-stage "Sauerbruch," or a two-stage "Brauer." As the compression from the latter is the greater of the two, it is indicated for those whose lesions are extensive, and whose general condition is sufficiently good to withstand the somewhat more severe operation. It will be found in a certain minority of cases operated upon by either technic, that the compression has not been sufficient to control the disease; this is especially true of thick-walled cavities and infiltrative lesions that are unusually stiff. It then becomes necessary to supplement the original operation by further removal of ribs posteriorly, or parasternally, or by pneumolysis. The most commonly used supplementary procedure is pneumolysis, which is an extrapleural separation of the lung and both of its pleuræ from the ribs, and a filling of the space created with a gauze tampon, or a fat graft, a paraffine "fill," or a pedicled muscle graft. When even these measures fail to collapse certain cavities, cavity drainage is indicated. Favorable mention has already been made of the use of phrenicotomy as a preliminary to any type of operation.

Partial Procedures. Resection of parts of ribs I to XI is known as the complete operation, in that it compresses an entire hemithorax and puts it at rest. Primary operations that compress only a part of a hemithorax (over the principal lesions) are termed partial procedures. They include resection of only the upper or lower five or seven ribs; pneumolysis; phrenicotomy.

Where the tuberculous lesions are apparently chiefly confined to the upper lobe, the temptation is great to limit the compression to that region and thus to save the lower lobe for function and so to spare the better lung any increased work that might activate a quiescent disease process there. Until very recent years this practice has been relatively common, but increasingly frequent reports of its unfavorable late results, and Sauerbruch's impassioned pleas against it, have combined to put it in disrepute, except for very particularly indicated cases. Sauerbruch, Brauer, L. Spengler and Saugmann, Jessen, Hauke and Goetze warn against it on the basis of their unfavorable results. Eloesser puts it neatly by saying that the complete operation should always be done primarily, for to trust to half-measures is often to lose the opportunity to control

the lesions during a favorable stage. Bull advises complete operation even if the disease seems to be limited entirely to the lower lobe; in such a case the *first* stage of the operation would be the resection of the *upper* ribs in order to prevent aspiration above. Gravensen, on the other hand, favors limiting the resections to the lower ribs if only the lower lung is diseased.

The principal objections to partial operations are: (1) abrupt compression of the most diseased portion of a lung squeezes out infective material, which is liable to be aspirated into that part of the same lung which is not compressed and is actively breathing, and disease spread. Sauerbruch has seen this occur not infrequently after partial procedures, and is now uncompromisingly opposed to them. Stöcklin says it occurs once in 100 cases. L. Spengler believes that not many of these cases of aspiration pneumonia have as yet been reported by publication. Baer personally has never seen a case of aspiration. While complete operation does not absolutely assure against aspiration, it very greatly reduces its incidence. Davies advises phrenicotomy preliminary to pneumolysis. (2) Brauer says that the lower lobe of a lung, in which surgical compression is indicated for upper lobe disease, almost always contains a few active tubercles, although they may not be demonstrable clinically; and that the extra work imposed upon such a lobe may determine a rapid advance of the disease there, so that a difficult and dangerous secondary operation, involving removal of regenerated bone in the field of the first operation, would then become necessary. Wilms and Sauerbruch would always compress the lower lobe, even if not apparently diseased. (3) Compression of only a part of one lung allows that part to "slip" to the unnarrowed space of the chest cavity, and the final effect is that the whole lung is relaxed, rather than the most diseased parts being actually compressed, and this is not so favorable for healing. This does not occur to such a degree if there are strong pleural adhesions, and if the mediastinum is well fixed for counterpressure. (4) If the continuity of any one or more ribs (ribs XI and XII excepted) remains uninterrupted, this rib, or ribs, acts as a support for the whole hemithorax and prevents its "settling" and compressing the lung as well as it does after a complete thoracoplasty. (5) As thoracic movement on the diseased side is only partially restricted, the flow of lymph into the general circulation is only partially checked (Jessen). (6) A ridge, which is the uppermost of the remaining ribs and marks the lower limit of an upper partial thoracoplasty, may become so painful as to require its removal, or the removal of all the remaining ribs.

Partial procedures, however, have certain advantages and rare indications. They are: (1) For patients whose lesions are limited to a small area, are non-progressive in character and have shrunk

to such a degree as to demand release of tension by resection of the resisting overlying bony cage; such patients, however, should not be producing more than 20 to 30 cc of sputum a day, else the danger of aspiration to the uncompressed part of the lung is considerable. For such cases Sauerbruch would be willing to resect only the upper ribs, although he would be strongly tempted to play safe and first section the lower ribs in order to check their movements, or he might first do a phrenicotomy. (2) Patients who are too sick to withstand the operative shock of the complete operation may bear a partial operation very well, and its favorable influence may justify the risks of the partial procedure. Its advantages in such cases are the less operative shock, less mediastinal displacement, less interference with circulation and respiration; postoperative cough and expectoration are easier. This last named advantage especially indicates partial operation for severe hemoptyses where the danger of spread of infection by aspiration is always great; for these cases Sauerbruch resects ribs I, II and III parasternally, performs a pneumolysis and places a snug gauze tampon. A phrenicotomy alone may check hemoptysis. (3) Certain patients may have so much active disease on the better side that the extra work that would be imposed upon it by a complete operation on the worse side would probably cause its rapid spread; in them partial compression on the worse side may bring about so much improvement of general resistance as to enable the better lung to heal itself, and then if the worse lung is still active; the operation may be safely completed. (4) Wilms would resect the three upper ribs on each side for strictly circumscribed, relatively inactive, bilateral apical disease, if it had marked fibrotic tendencies and if there were very little sputum.

Further description of pneumolysis and of phrenicotomy will be found below; where they are discussed as operations supplementary to thoracoplasty.

VII. Preoperative Management. Saugmann and Madinier strongly advise that all operations for pulmonary tuberculosis be performed at suitably equipped sanatoria and not at general hospitals, which are usually in the city, and to which patients with little reserve strength must be transported, and where the conditions are rarely favorable for suitable tuberculosis régime.

If operation has been decided upon and there is some question as to the functional validity of the heart, a preoperative course of digitalis is to be highly recommended.

Bed rest for at least two weeks is advisable for patients who present themselves for operation with a simple chronic bronchitis; inhalants and expectorants may prove of use.

A very important prophylactic measure against aspiration of infected secretions, especially from cavities, during operation is to insist that the patient "empty his lung" two hours, and again one

hour before operation; this he does by assuming the position, best known to himself, that enables him to cough up all loose sputum in a few minutes. Sometimes the best position is leaning over the side of the bed, to drain the sputum by gravity; sometimes lying on the better side and sometimes on the worse.

Broad experience has taught both Sauerbruch and Jessen to fear greater preoperative doses of morphin than $\frac{1}{6}$ gr. (0.0108 gm.) when a local anesthetic is to be used in addition; they fear synergistic action.

Other preoperative preparation does not differ from that used for general major surgery.

VIII. Anesthesia. Choice of anesthetic is somewhat influenced by national custom. For general narcosis ether, or ether-chloroform mixture is commonly used on the continent; nitrous-oxide-oxygen in America. In all countries, however, regional and local anesthesia is used most, or in connection with general narcosis. Sauerbruch and Bérard would refuse to operate at all if a patient were found to be hypersusceptible to a combination of morphin and novocain, and whose heart or great amount of sputum contraindicated general narcosis.

Sauerbruch's preference is for straight ether whenever there are less than 30 cc of sputum a day (or a little more than this if it can be well evacuated just before operation); its use upon many hundreds of patients with active pulmonary tuberculosis has convinced him that it has no unfavorable action on the lungs, unless by abolishing the cough reflex it allows aspiration of secretions. This, of course, would hold for a like degree of narcosis with any other general anesthetic, and sudden groaning or crying under an imperfect local anesthesia may also be responsible for aspiration. As a great majority of cases for thoracoplasty have more than 30 cc of sputum per day, Sauerbruch is obliged to use regional and local anesthesia far more often than general, and to his regret as he has learned to fear the toxic action of the amounts of novocain required for these operations. He has seen a fatal case of poisoning from novocain, and 2 cases of dangerous collapse from which there was recovery within twenty-four to forty-eight hours, and a number of cases of mild poisoning. At first he attributed the symptoms of this collapse—pallor, light cyanosis, sweating, slow then fast pulse, cold nose, hiccough, vomiting—to operative shock, but experience has showed him that there is a difference, and that when the indications for operation are properly placed there is almost no true operative shock.

Sauerbruch limits himself to 0.9 gm. of novocain, and to this amount he adds 0.001 cc of adrenalin chloride; he makes the solutions isotonic with the blood, as anesthesia then lasts longer. He infiltrates the line of incision with 50 cc of 0.5 per cent solution,

using a 12 cm. long needle; then by the Schumaker technic he injects 5 to 6 cc of a 1 per cent solution around each of the intercostal nerves at the rib angles. Except in rare cases he is able to obtain practically complete anesthesia. Archibald recommends injecting each intercostal nerve, after the ribs have been exposed, at two or three points near the rib angle in order to increase the chances of obtaining complete anesthesia. Saugmann found it more accurate to inject the anesthetic around the intercostal nerves after the skin-muscle incision had been made. Baer does this for the upper nerves, as he fears he might wound the pleura or lung and thereby spread infection, if he attempted to reach them all the way from the skin; Guilliminet recommends diffusing the anesthetic solution by gently stroking the tissues over the place of injection. Davies has suggested the use of anoci-association. Shumacker was able to produce perfect regional anesthesia in only 14 of 35 cases. In addition to his cases of poisoning Sauerbruch has reported 2 fatal accidents; one was a suppurative mediastinitis consequent upon carrying infection on the needle from latent infection in the pleura; the other was a ruptured aneurysm which was started by a wound from the anesthetizing needle.

Saugmann always tested the patient's susceptibility to novocain a few days before operation. He reported a death following the use of 190 cc of a 0.5 per cent novocain, plus 0.015 gm. morphin one-half hour before operation. He always tried to limit himself to 150 cc of 0.5 per cent solution, and set 200 cc as the absolute limit. Where there is only a small amount of sputum he would not hesitate to use a little ether. Eloesser and Bull also warn against hypersusceptibility to novocain.

Stöcklin reports a death from the use of 1.2 gm. novocain, and now uses morphin and scopolamin and from 0.5 to 0.7 gm. novocain. Lorey uses as much as 150 to 200 cc 1 per cent solution, and Bull up to 300 cc 0.5 per cent plus 50 to 75 cc 1 per cent. Willy Meyer reports a death in forty-eight hours, probably from novocain poisoning; he now fears the Kappis method of injecting the anesthetic in the region of the intervertebral foramina, and will use only the Shumacker technic of injecting near the rib angles. Meeker and Frazer conclude from a study of regional-local anesthesia in 4000 general surgical cases that 1.5 to 2 gm. 0.5 per cent novocain-adrenalin solution are safe for local infiltration, or 1 gm. of 1 per cent novocain-adrenalin is safe for nerve block. Bérard is pleased with the use of anacain, which is used with adrenalin in the same strengths as novocain; as much as 1.2 gm. may be employed. Its great advantage is that it maintains anesthesia for thirty-six to forty-eight hours; this covers the most painful postoperative period, and further, permits the injection of the anesthetic to be made an hour or so before the operation.

(To be continued)

REVIEWS.

A DIABETIC MANUAL FOR THE MUTUAL USE OF DOCTOR AND PATIENT. By ELLIOTT P. JOSLIN, M.D., Clinical Professor of Medicine, Harvard Medical School, Consulting Physician, Boston City Hospital. Third edition. Pp. 211; 17 illustrations. Philadelphia: Lea & Febiger, 1924.

THE close coöperation that the physician who is treating diabetes has with his patient is seen in almost no other disease, and probably in no other disease does the physician go to the same extent to teach the individual about the disease, as in diabetes. For this reason any book which explains in simplified language just what the diabetic is to do is of great service in aiding patient and physician in understanding and in following out the course of the disease. For this reason several books of this type now on the market are extremely popular, but the one in question has always been among the most popular, probably because of the fame of the author as a diabetic specialist as well as the deep scientific knowledge that he possesses and which he is able to present to the public in a way which appeals most thoroughly. This little book of Joslin's is excellent in every way. It needs no introduction to the medical profession, and the profession can always feel that it is the most satisfactory book of this type on the market. M.

MEDICAL AND SANITARY INSPECTION OF SCHOOLS FOR THE HEALTH OFFICER, THE PHYSICIAN, THE NURSE AND THE TEACHER. By S. W. NEWMAYER, A.B., M.D., Supervisor of School Medical Inspection, Philadelphia. Second edition. Pp. 462; 79 illustrations and 6 plates. Philadelphia and New York: Lea & Febiger, 1924.

A NUMBER of modifications have been made in the original text, to keep abreast of recent developments in the various fields of school inspection. The book as it stands is a practical and comprehensive handbook which will highly commend itself to officials whose care is the health of school children. A.

TUBERCULOSIS OF THE LARYNX. By SIR ST. CLAIR THOMSON, M.D., F.C.R.P., F.R.C.S. Pp. 91; 7 illustrations. London: Medical Research Council, 1924.

THIS is a very complete exposition of the subject. It goes into detail concerning various phases of laryngeal tuberculosis and is compiled with the usual thoroughness of the work put out by the Medical Research Council. It is a most complete exposition by one who has seen and observed with a critical mind many cases of tuberculosis of the larynx. M.

DIFFERENTIAL DIAGNOSIS. Vol. II. By RICHARD C. CABOT, M.D., Professor of Medicine and Professor of Social Ethics at Harvard University; formerly Chief of West Medical Service at the Massachusetts General Hospital. Third edition. Pp. 709; 254 illustrations. Philadelphia: W. B. Saunders Company, 1924.

THE third edition of this well-known, unusual presentation of differential diagnosis remains essentially unchanged from that of the previous editions in form, in material presented and in the case histories. The introductory discussion, however, has been changed somewhat and, to use the hackneyed expression, the book has been brought up to date. To those of the medical profession not familiar with this particular book by the author it may be said that it is an extremely interesting presentation of the subject of differential diagnosis. It makes extremely smooth and easy reading, as would be expected from one who has the gift of writing as has the author; and because of this ease of expression the reader unconsciously learns a great deal while perusing the book which he would otherwise miss in a presentation less clear and less succinct.

M.

DIPHTHERIA. ITS BACTERIOLOGY, PATHOLOGY AND IMMUNOLOGY. By FREDERICK W. ANDREWES, WILLIAM BULLOCH, S. R. DOUGLAS, GEORGES DREYER, A. D. GARDNER, PAUL FILDES, J. C. G. LEDINGHAM and C. G. L. WOLF. Pp. 544; 6 illustrations. London: Medical Research Council, 1923.

THE present monograph published by the Medical Research Council is a decided departure from the usual presentation of a scientific subject. It is the work of seven men, each one of whom, although contributing only special chapters, has gone over in detail the other chapters, so that they have become collectively

responsible for each chapter. The literature of diphtheria has been gone over most thoroughly. Every reference available on the scientific side of the disease has been utilized and each article has been critically read. Those that were of no value were discarded, whereas the valuable ones were incorporated in the work. The number of articles that were utilized may be appreciated by the fact that there are over a hundred pages of references in the bibliography. In addition to this very complete critical review of the literature of diphtheria, the authors have been enabled by the British Medical Research Council to take up research problems in order to elucidate, if possible, work which was incomplete or fill in the gaps in our knowledge. In this way the Committee on Publication has brought together a monograph which seems to be the ultimate in completeness. That it will be of great value to the research worker and the scientist as well as the medical profession in general goes without saying. The reviewer is most enthusiastic about the work, and trusts that the Medical Research Council will in the future take up in the same way other of the acute infectious diseases.

M.

DICTIONARY OF BOTANICAL EQUIVALENTS. By ERNST ARTSCHWAGER, PH.D., Instructor in Plant Physiology, Cornell University; and EDWINA M. SMILEY, M.A., Instructor in Plant Pathology, Cornell University. Pp. 137. Baltimore: Williams & Wilkins Co., 1924.

THIS small dictionary is especially for the use of the botanist and the pharmacologist. It contains the German and French terms with their English translation. A needed dictionary is now added to the list of standard dictionaries.

M.

THE ENDOCRINE ORGANS. Part I. By E. SHARPEY-SCHAFER, LL.D., D.Sc., M.D., F.R.S., Professor of Physiology, Edinburgh University. Second edition. Pp. 175; 86 illustrations. New York: Longmans, Greene & Co., 1924.

THE first portion of this work which is now making its appearance discusses diseases of the thyroid, parathyroid and suprarenal. This second edition, appearing nine years after the first edition, is very thoroughly revised, so fully, indeed, that it might almost be considered a new treatise on the subject of endocrinology. The book is a physiological rather than a clinical study, and deals with physiological experiments rather than hypothetical results in the

treatment of presumed endocrine disorder. Definite proof is brought for every statement that the author makes, and hence the work is authoritative to the fullest extent. M.

PATHOLOGISCH-PHYSIOLOGISCHE PROPÄDEUTIK. By MAX BURGER, a.o. Professor der inneren Medizin und Oberarzt an der med. Universitäts Klinik Kiel; with a foreword by A. SCHITTENHELM, Direktor der Klinik. Pp. 342; 27 illustrations. Berlin: Julius Springer, 1924.

RECOGNIZING Krehl's celebrated book on pathological physiology as unique of its kind, the author of this new book aims for a new goal, namely, to offer to students and young doctors an introduction into pathological physiology which will clarify the difficult problems of the clinic and its borderline. In the present instance, however, this is largely a distinction rather than a difference, as much the same topics are taken up in much the same way as in Krehl's book. To be sure, a few more subjects are considered (functional disturbances of endocrines, liver, spleen, skin and organs of locomotion), but to offset this the others are treated less thoroughly, in poorer sequence and not so well. In the section on diabetes the only mention of insulin is a reference to MacLeod's paper on the fish source of insulin, which is cited from a 1923 German referate; in the section on the hypophysis no mention is made of the recent work on the relation of the hypothalamic region to hypophyseal symptoms and in fact only one reference is less than ten years old; in the section on the spleen the references are without exception to German authors and make many assertions which are incorrect or, at best, quite undecided. We agree with the introducer that Krehl's book remains in its former position.

K.

APPLIED PATHOLOGY IN DISEASES OF THE NOSE, THROAT AND EAR. By JOSEPH C. BECK, M.D., F.A.C.S., Associate Professor of Laryngology, Rhinology and Otology, University of Illinois, College of Medicine. First edition. Pp. 280; 268 illustrations. St. Louis: C. V. Mosby Company, 1923.

To the average medical reader the term "applied pathology" is not a very definite concept and the book under review will not contribute toward its clarification. The author's method has been to consider in twelve chapters one hundred and twenty acute and chronic diseases of the nose, throat and ear, in sections varying

from a paragraph to several pages in length. Usually the only subheading is "Treatment," but in a few "Gross Pathology" (which not infrequently wanders into symptoms and so forth), and even "Histopathology" and "Application" are segregated. Except for this and a rather liberal use of photomicrographs, the book would be more accurately described as an incomplete text-book on the subject. The complaint of incompleteness is met in the foreword by the author's expressed "desire to limit this work almost exclusively to my personal experience." K.

LOUIS PASTEUR. By S. J. HOLMES, PH.D., Professor of Zoölogy, University of California. Pp. 246; 14 illustrations. New York: Harcourt, Brace & Co., 1924.

THIS small biography of Pasteur, as the author remarks in his preface, is in no way an attempt to offer anything new to what has already been written, but it does present in a simple informative and pleasing manner the important milestones in the life of this great man. It may be read with enjoyment by any individual who has the slightest knowledge of any type of science, or by one who is interested in science. M.

OUTLINES OF MEDICAL HYDROLOGY. By R. FORTESCUE FOX, M.D. Pp. 136; 10 illustrations. London: J. and A. Churchill, 1924.

HYDROLOGY is a branch of therapeutics which is very extensively neglected in this country. It might be well for practitioners to look over the series of lectures by the author, delivered at the University of London, which describes in detail the various types of baths and their indications. The book is well written and conservative, and the author does not claim success in every type of disease or disorder, as do so many of the men who ride therapeutic hobbies. M.

MANAGEMENT OF DIABETES. By GEORGE A. HARROP, JR., Associate in Medicine, College of Physicians and Surgeons, Columbia University and Assistant Visiting Physician, Presbyterian Hospital, New York. Pp. 176. New York: Paul B. Hoeber, Inc., 1924.

HARROP has summarized the clinical instruction and laboratory instruction that has been given at the Presbyterian Hospital in

New York to physicians unacquainted with the use of insulin. He has put this information in a more complete form than any of the small books on diabetes with which we are acquainted, and he has given extremely wise advice to the physicians. Included in the book are almost fifty pages of diabetic recipes, as well as a rather unusual summary of food values of the standard foods. The tyro in the handling of diabetes can well profit by a close study of this most agreeable presentation of the subject.

M.

HEMORRHOIDS, THEIR ETIOLOGY, PROPHYLAXIS AND TREATMENT BY MEANS OF INJECTIONS. By ARTHUR S. MORLEY, F.R.C.S. (ENG.), late Temporary Assistant Surgeon to St. Mark's Hospital for Cancer, Fistula and Other Diseases of the Rectum. Pp. 114. London: Henry Frowde, Hodder & Stoughton, 1924.

THIS book is devoted to the thesis that the best treatment for uncomplicated internal hemorrhoids is by the injection method. Its contents, therefore, are rather controversial than judicial. He apparently has no extended experience with operation to parallel his large series of injections and in handling the statistics from St. Mark's Hospital in London; as to the mortality and morbidity of operation, he fails to point out that many of these cases were severe and of a type unsuited for injection. The book really serves to reiterate what was already known, that under proper precautions simple internal hemorrhoids can be successfully treated in many cases by injection.

P.

THE CIRCULATORY DISTURBANCES OF THE EXTREMITIES, INCLUDING GANGRENE, VASOMOTOR AND TROPHIC DISORDERS. By LEO BUERGER, M.A., M.D. Pp. 628; 192 illustrations. Philadelphia and London: W. B. Saunders Company, 1924.

IN recent years considerable new material upon the circulation of the extremities has made its appearance. Direct microscopic examination of the capillaries has been found to be a useful and simple procedure; studies upon the anatomy and physiology of these vessels have been published by Krogh and others, and the role of the sympathetic and autonomic nervous systems in circulatory disturbances has been extensively studied. These and other studies have resulted in a renewal of interest in Raynaud's disease, Buerger's disease, erythromelalgia and other circulatory diseases of the extremities. The author has gathered from widely divergent sources the best available data upon these subjects, and assembled them into

a book which in addition to being readable, is a veritable storehouse of information. This book constitutes a distinctly valuable contribution by one whose authority in this field will hardly be questioned.

A.

AIDS TO MEDICAL DIAGNOSIS. By ARTHUR WHITING, M.D., Senior Physician to the Prince of Wales' General Hospital, Tottenham, London, and late Physician to the Mount Vernon Hospital for Consumption and Diseases of the Chest. Pp. 177; 16 illustrations. Third edition. New York: William Wood & Co., 1924.

THIS little book is replete with practical points in the diagnosis of the usual conditions which a medical student meets in the wards and dispensaries. The author makes no attempt to discuss systematically the various diagnoses, but does give the more asserting features in the several diseases.

M.

DIABETES. By PHILIP HOROWITZ, M.D. Second edition. Pp. 219; 34 illustrations. New York: Paul B. Hoeber, Inc., 1924.

THE reviewer has employed the small book of the author's for several years, and has found the previous edition extremely valuable not only for his own use, but also in letting diabetic patients with sufficiently educated minds read it over to their own great advantage. The new edition, of course, contains the more important additions brought about by the introduction of insulin in the therapy of diabetes.

M.

BULLETIN NO. X OF THE INTERNATIONAL ASSOCIATION OF MEDICAL MUSEUM. Pp: 165; 39 illustrations. New York: P. B. Hoeber, 1924.

THE bulletin of this Society, which is also a journal of technical methods, is under the editorial management of Dr. Maude Abbott and Major Coupal. It contains not only general and special articles on gross and histological morbid anatomy, but also an experience department, valuable sections on museum, bacteriological, microscopic and photographic technic, amplified by abstracts of the current literature on these topics. The list of members shows its truly international character, and it is hoped that the European sections will soon become as active as their American and Canadian confrères.

K.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI,
CINCINNATI, OHIO.

Rectal Digitalis Therapy.—LEVY (*Arch. Int. Med.*, 1924, 33, 742) reports a series of 19 patients with auricular fibrillation and 1 patient with ectopic auricular tachycardia, to whom an aqueous solution of purified extract of digitalis leaves was given by rectum in doses ranging from 8 to 20 cc. Unmistakable initial effects on the heart-rate was noticed in an average time of two hours and thirty-five minutes. The average time of maximum effect was reached in nine hours and thirty minutes. The initial effect was seen on an average in two hours and a half. The author reports that in every case a desirable therapeutic effect was obtained. In some of the patients results were dramatically rapid. While the author says that this type of therapy is intended to supplement, not supplant, the oral method of administration, and is useful in cases with nausea and vomiting, he intends to convey the meaning that the nausea and vomiting must be due to some cause other than the result of the digitalis therapy, for it is well known that the effect of digitalis is central and not peripheral and digitalis nausea may occur after the administration of digitalis by any method. After a surgical operation in a patient who has need of digitalis the rectal administration of the drug is most satisfactory.

A Study of Mixed Leukemia, with the Report of a Case.—The occurrence of mixed leukemia is extremely rare, so rare indeed that some hematologists doubt if there is such an entity. LOGEFEIL (*Arch. Int. Med.*, 1924, 33, 659) has what he believes to be another one of the rare cases which have been rarely described. He appreciates the fact that some hematologists question the possibility of there being a true

mixed leukemia, and he discusses this fully in his case report, in which the blood smears as well as the histological study of the tissues showed activity of both myeloid and lymphoid systems. While hematologists quite generally do recognize the possibility of such occurrence, nevertheless it must be borne in mind in such a case as the author's, occurring as it did in a small child, that a marked lymphoid reaction is very frequent in children and that this reaction may be sufficiently severe as to lead one to the opinion that leukemia is present.

A Hitherto Undescribed Form of Valvular and Mural Endocarditis.

—LIBMAN, whose work on endocarditis needs no introduction to the medical profession, and SACKS (*Arch. Int. Med.*, 1924, 33, 701), in a long and complete paper, discuss fully a new type of endocarditis. The importance of their contribution make it necessary to include a summary of their results: "We have had the opportunity of studying the clinical and pathological findings in 4 cases of a hitherto undescribed form of endocarditis, which we have for the present described as an atypical form of verrucous endocarditis. In morphology and localization the endocardial lesions differed from those observed in subacute bacterial, rheumatic and other types of endocarditis. All four valves were involved, and there was a tendency for the inflammatory process to attack the mural endocardium. A uniform finding in our cases was the extension of the endocarditic process from the ventricular aspect of the posterior cusp of the mitral valve along the adjacent mural endocardium of the posterior wall of the ventricle. Isolated areas of mural endocarditis were found in the right auricle and both ventricles. The vegetations were free of demonstrable bacteria, and presented a histological structure which differed in many respects from that of the lesions in other types of endocarditis. The heart muscle showed neither Aschoff bodies nor Bracht-Waechter lesions, and the kidneys showed no embolic glomerular lesions. The disease, in the form in which it attacked young people who had previously had no organic symptoms, ran a subacute course with fever and progressive anemia. Briefly enumerated, the clinical findings were pericarditis, white-centered petechiæ, arthritis, erythematous and purpuric rashes, ulcerative lesions of the mucous membranes, pleuropulmonary symptoms, embolic phenomena, enlargement of the liver and spleen, acute glomerulonephritis, a tendency to leukopenia and repeatedly negative blood cultures. Two of the patients had an eruption on the face which resembled acute lupus erythematosus disseminatus. One of the patients is said to have had tender erythematous nodules, which were apparently identical with the Osler nodes, previously observed only in subacute bacterial endocarditis. For reasons stated above the acute pericarditis, white-centered petechiæ and negative blood cultures together appears to have diagnostic value, especially in differentiating these cases from rheumatic and subacute bacterial endocarditis. In certain cases the chief diagnostic problem appears to be the detection of endocarditis, for the manifestations of the latter may be masked by other symptoms. In such cases the presence of an eruption on the face resembling acute lupus erythematosus disseminatus or peculiar erythematous and purpuric rashes else-

where should lead to a search for the other manifestations of the atypical form of endocarditis. Attention was directed to the similarity of certain of the symptoms to those observed in the erythema group of Osler and to the existence of a possible relationship between certain instances of the latter and the atypical form of endocarditis. The frequency of the disease and the ultimate outcome of non-fatal cases is a matter of conjecture. Future studies must determine whether this form of endocarditis is a potential cause of chronic valvular disease. The etiology is as yet unknown, and it is suggested that in future studies the special methods adopted for a cultivation of filtrable viruses and spirochetes be employed among others in the search for the exciting agent."

A Study of the Mechanism of Absorption of Substances from the Nasopharynx.—BLUMGART (*Arch. Int. Med.*, 1924, 33, 415), using the method by which Meed demonstrated the passage of the cerebrospinal fluid into the lymphatics of the brain has been able to show a rapid absorption of crystalloid, colloid, and certain forms of particulate matter through the olfactory epithelium. The route of passage of the absorbed substances be found to be only along the olfactory nerve cells into the region of the lymphatics. These experimental findings accord well with those on the mode of infection in meningitis and poliomyelitis. It is suggested that such ready absorption along the olfactory cells is a physiological adaptation to bring to these cells the substances of the air which we are to perceive through our sense of smell.

Studies on the Respiratory Mechanism in Lobar Pneumonia: A Study of Lung Volume in Relation to the Clinical Course of the Disease.—BINGER and BRAU (*Jour. Exper. Med.*, 1924, 39, 677) studied the functional residual air in a series of normal patients and in 10 patients with lobar pneumonia at different stages of the disease. Their purpose in mind was to obtain data concerning the relationship in pneumonia between the extent and progress of pulmonary involvement, the occurrence of dyspnea and cyanosis and the changes in lung volume. A constant relationship was found to exist between the persistence and disappearance of symptoms (fever, accelerated heart-rate, rapid and shallow breathing, cyanosis) and fluctuations in the functional residual air. The residual air was found to be decreased whenever the above symptoms persisted, while it rose toward normal as they disappeared. This rise was usually to be noticed soon after the crisis. The reduction in residual lung volume was also found to parallel the alterations in physical signs and radiographical shadows. As these pathological signs cleared up the residual lung volume returned toward normal. From the time of onset of the disease eleven to twelve days were required, on the average, for the functional residual air to become constant in the cases which recovered.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND
ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES
IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SUR-
GEON TO THE PHILADELPHIA GENERAL AND
NORTHEASTERN HOSPITALS.

Results of Treatment following Compound Fractures Occurring in Civil Life.—Cook (*Jour. Bone and Joint Surg.*, 1924, 6, 93) says that death occurred in 3 cases by the method of aseptic occlusion; 2 of septicemia and 1 of a gas bacillus infection. Under this method, a leg was amputated in 2 cases for chronic osteomyelitis. In the cases treated by drainage, gas-bacillus infection developed in 1 case, and the leg was amputated. In the cases treated by the Carrel-Dakin method, it was necessary to amputate a limb in which gas-bacillus infection was present. In the cases treated by débridement and suture, 2 patients, both of whom were completely débrided, died from a gas-bacillus infection, and in 2 patients with gas-bacillus infection it was necessary to amputate a limb. When wounds are found to be infected by streptococcus, it is necessary to open the wound widely and desirable to treat the wound by the Carrel-Dakin method. Osteomyelitis is more common in those cases treated by aseptic occlusion drainage and incomplete débridement. The time which the patient must spend in the hospital is shortest under the method of débridement and suture, when successfully done.

Experiences in Rectal Surgery.—GORDON-WATSON (*Brit. Med. Jour.* 1924, 1, 559) says that the absence of sensibility to pain in the rectum has disadvantages in disease, especially since a malignant growth provided it does not pass the boundaries of the rectum by invasion may grow to considerable size without the owner's knowledge. It often happens that rectal pain is reflex in character, due to simple prostatic enlargement. It is a matter of regret that pain is generally regarded by the public as inseparable from cancer. It is common medical knowledge that cancer of the rectum is painless in its earlier stages. When treated by radical excision in this stage, the percentage of cure is probably higher than for any other part of the body, except perhaps the lower lip. Inflammatory strictures are constantly mistaken for malignant disease. A breaking down hematoma has been mistaken by the author for carcinoma. The author studied a series of 75 cases of fistula in ano, for tuberculosis, by microscopical sections and guinea-pig inoculations. Ten proved to be tuberculous, 5 of them were victims of active pulmonary tuberculosis and 5 showed evidence of tubercle elsewhere and must be regarded as cases of primary tuberculous fistulæ. Nine of these 10 cases were operated and after six months only 1 of them had healed. The author decries the bad name that colostomy suffers.

He feels that the secret of management in these cases lies in a regular daily washout, which trains the colon to act automatically, efficiently and thoroughly once in twenty-four hours.

The Treatment of Malignant Growths about the Face.—WITHERS and RANSON (*Colorado Med.*, 1924, 21, 92) say that it has been observed that the more embryonal or undifferentiated the type of cell, the greater is its radiosusceptibility and conversely the more differentiated, highly specialized the type of cell, the greater is its radioresistance. Cells containing large amounts of chromatin in the nucleus are more easily killed than those containing little chromatin. It is common knowledge that the endothelial lining of blood and lymph vessels is very radio-sensitive. Tumors having an abundance of thin walled delicate capillaries react much more quickly and favorably to radiation than corresponding tumors having a scanty blood supply. The cellular reaction to radiation depends upon the amount of radiant energy absorbed, whether it be primary or secondary. The susceptibility to short length therapy is a cellular characteristic, depending upon a definite histological structure. The normal tissue reaction to radiation and neoplastic invasion depends to a large degree upon the well-being of the body as a whole. There is sufficient data to predicate on *a priori* grounds those tissues or tumors which will prove radioresistant or radiosusceptible. The use of the radium or roentgen-ray in a given condition should require an equal amount of surgical judgment, a more complete knowledge of the pathology and a broader biophysical training than the corresponding surgical oblation demands.

Spondylolisthesis a Common Lumbo-sacral Lesion.—BOWMAN (*Am. Jour. Roent. and Rad. Therap.*, 1924, 11, 223) says that spondylolisthesis is not an uncommon condition. It is a common cause of pain in the lower back, as shown by the frequency with which it occurs in lower back injuries. It is usually the result of trauma, the injury often being considered of minor importance. The symptoms are often not so severe as you would expect this type of lesion but are prone to get progressively worse after injury. Many of the cases now diagnosed as sacroiliac dislocations by the attending physician or surgeon that cannot be demonstrated roentgenologically are in reality, cases of spondylolisthesis. Clear detailed lateral roentgenograms of the lumbo-sacral region are absolutely essential in diagnosing these cases.

Acute Appendicitis in Childhood.—BEEKMAN (*Ann. Surg.*, 1924, 79, 538) says that the earlier the diagnosis is made and operation performed, the lower is the mortality, the fewer the complications and the shorter the convalescence. The condition in children is more frequent as adolescence is approached. With the exception of children under five years of age, in whom it is extremely high, the mortality is about the same as is found among young adults. The disease is found twice as commonly in boys as in girls, while the mortality is twice as great among girls as in boys. Perforation of the appendix with spreading peritonitis or abscess formation occurs more often in children than in adults. Immediate postoperative complications are as commonly found in children as in adults with the exception of secondary

abscesses, which are seen more often. Incisional hernia follows operation in children more often than in adults. Sloughing of muscles and aponeurosis, secondary abscesses and partial evisceration of portions of the abdominal contents appear to be the causative factor. Mistakes in diagnosis would seem to be inevitable, and it would be better to err by operating.

Fracture of the Anterior-superior Spine of the Ilium by Muscular Violence.—CARP (*Ann. Surg.*, 1924, 79, 551) says that the fracture is infrequent, 21 cases being reported. All the patients were males, a large percentage of whom were athletic and muscular. All had pain, while a snapping was felt by 45 per cent. The fragment was felt in 90 per cent. All the patients limped, 76 per cent had immediate disability, 11 per cent walked a short distance, 1 case could walk forty-eight hours later and 1 case walked about for three weeks. The majority of the cases were right-sided. The average duration of the disability in the 9 unoperated cases was twenty days. The two operated cases showed return of function in one month. End-results were excellent in all cases.

Congenital Hypertrophic Pyloric Stenosis in Infants.—COCHRAN (*California and Western Med.*, 1924, 22, 137) states that ether anesthesia is preferable to local. The Fredet-Rammsted operation is much simpler and more quickly performed than gastroenterostomy, and therefore the best technic to follow in all cases. In most cases the differentiation between pylorospasm and stenosis is clear and only in questionable cases should fluoroscopic aid be resorted to. These little patients are too sick to be loaded up with barium, unless it is absolutely necessary. Cases under observation should not be allowed to lose too much weight before resorting to surgery for after loss of 20 per cent of body weight these cases become poor risks instead of good risks. The simpler technic and earlier operating has reduced the earlier greater mortality of gastroenterostomy series.

The Treatment of Acute Empyema.—CHANDLER (*St. Barth. Hosp. Rep.*, 1924, 57, 49) says it appears that the resection of a rib is a satisfactory method in adults, but too severe a procedure in children. The invention of new and ingenious methods of treating empyema has a peculiar fascination, and there is a great temptation to regard the favorite modification as a great advance. Recent work in chest surgery has taught much. Positive and negative pressure chambers have been discarded. The lung can be handled freely. Though compressed for many months, it can be liberated and restored to perfect function by the stripping of the thick pleura that has held it prisoner. By operating neither too late nor too soon, by freeing the lung that is bound down, by leaving no large irritant in the pleural cavity such as an unnecessarily long drainage tube, there is every reason to look for success in the great majority of cases. If the empyema has been left for a long time and the lung is bound down, immediate decortication is a more rational procedure than suction drainage, and an extended trial will probably prove it the more successful method. The figures relating to all the methods employed in the treatment of empyemata occurring in the first year of life make the prospects at this age seem very hopeless.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,
NEW YORK.

The Treatment of Asthma with Combined Peptone and Vaccine.—VEITCH (*Brit. Med. Jour.*, January, 1924, p. 13) found that some cases of asthma did not react to either peptone or vaccines when given alone, so devised a system of giving the peptone and vaccine combined. His results in 24 cases treated in this manner were unsatisfactory, and no other medicinal or dietary treatment was used. The solution used was in three strengths: A. 5 cc of a 5 per cent solution equal to 0.25 gm. of peptone plus 235,000,000 organisms of an anticatarrhal vaccine of mixed strains of bacteria; B. 5 cc of a 10 per cent solution equal to 0.5 gm. of peptone plus 940,000,000 organisms of an anticatarrhal vaccine of mixed strains of bacteria; C. 10 cc of a 10 per cent solution equal to 1 gm. of peptone plus 1,880,000,000 organisms of the same anticatarrhal vaccine of mixed strains of bacteria. Injections were given every seven days. For the first four weeks half a tube of A solution per week, for the second four weeks half a tube of B solution per week, and so on, increasing in strength of dosage. The older the patient the more stubborn was the case to treatment, and the younger the patient the sooner were the signs of improvement noticed.

Further Observations on the Action of Iodid in Goiter.—JAGIC and SPENGLER (*Wien. klin. Wchnschr.*, 1924, 5, 16) conclude that good results in cases of goiter can only be obtained by close observation of the patient, and strict individualization in the dosage of sodium iodid. In general the diffuse forms are more amenable to treatment than the nodular. Weekly observation of cases was made to determine the circumference of the neck, the body weight and the appearance of cardiovascular symptoms. Three drops of a 5 per cent sodium iodid solution were given three times a day in increasing doses. In 16 cases of goiter with thyrotoxic symptoms 8 were improved, 6 remained unimproved, and 2 showed increase of symptoms. In most cases the dose could not be increased above 5 drops three times a day. Of 36 cases of goiter without thyrotoxic symptoms 12 were improved, 17 remained unimproved and 7 cases developed conditions which indicated stopping treatment. One case of this series took 10 drops three times a day, and one 15 drops three times a day. The greatest change in the size of the goiter was also obtained in this group. Only 5 cases with marked symptoms of Basedow's disease were treated. Two showed marked improvement, particularly in the size of the thyroid gland, 2 showed increased symptoms of the disease except for a diminution in the neck circumference, while the fifth showed no improvement, and was operated on.

New Uses for Suprarenin in Clinic and Practice.—The idiosyncrasy of the patient and the variation in the activity of various suprarenal extracts still restrict the more general use of extracts of the suprarenal gland in practice. MOEWES (*Deutsch. med. Wchnschr.*, 1924, 51, 239) recommends suprarenin (Höchstes Farbwerke) in 1 to 1000 solution for reliability and constant strength. Suprarenin has been used universally to raise blood-pressure and as a cardiac and vasomotor stimulant. In the last few years it has been used extensively to counteract the symptoms which sometimes arise following injections of arsphenamine. Conditions associated with or due to abnormal irritability of the vegetative nervous system, such as urticaria, erythema and local swelling are also corrected by injections of suprarenin; 0.25 to 0.5 cc, given subcutaneously or intramuscularly, is enough to obtain the desired results in most of these conditions. In the vomiting of pregnancy, and when of pure nervous origin, excellent results have been obtained by giving 20 drops three times a day by mouth—in spite of theoretical opposition to this form of administration. Injections of 0.25 to 0.5 cc are also indicated in these cases. The vomiting and headaches following lumbar puncture have also been relieved by similar injections. Nervous disturbances of the gastrointestinal tract are also influenced by injections of suprarenin and spasm is relieved, as is also done by atropin and papaverin. In cases of chronic asthenia, such as Addison's disease, continued injections should be given, and also in cases which show real or so-called pseudovagatonic manifestations. Serious conditions have never been seen with the small doses recommended by the author.

The Present Position of Blood Transfusion.—NATHER (*Wien. klin. Wchnschr.*, 1924, 37, 203) concludes from one hundred and fifty transfusions, which he has performed in the last year and a half, that avoidance of serious reactions during or after the transfusion can be accomplished by careful grouping of the donor's and patient's bloods, using the Moss grouping and the paraffined Percy syringe for the transfusion. He emphasizes the danger to the patient if the donor's blood cells are agglutinated. Defibrinated or citrated blood transfusions, he believes, should be discarded. The object of transfusion may be: (1) Addition of blood; (2) stimulation of the bone-marrow; (3) to stop bleeding; (4) foreign protein action, or the action of an immune substance. Results with acute hemorrhage are excellent and immediate secondary anemias are benefited not only by addition of blood to the circulation, but by stimulation of the bone-marrow, and he emphasizes the social importance of this fact for the wage-earner. In pernicious anemia it is an important preliminary to removal of the spleen. More than one transfusion is often indicated. He mentions the importance of transfusion as a hemostyptic in cases of persistent bleeding, particularly from the gums or from an ulcer of the stomach. Chronic septic processes are improved, and often can be cleared up by transfusion. A new indication first advocated by Professor Clairmont is the treatment of gastric ulcer, and the author mentions a case of inoperable ulcer of the cardiac end of the stomach in which a protracted bleeding was stopped, and pain ceased so that the patient could return to work. Cases of carcinoma which he has seen improved by transfusion he attributes to the improvement of the sepsis and the action of the blood as an immune body.

Pluriglandular Obesity and Its Treatment.—Obesity, due to pluriglandular dysfunction, may occur before or after puberty, but is usually seen in women following childbirth, immediately before or after the climacteric, or after some psychic disturbance. In all cases there is marked swelling of the fatty tissues, with a predilection for the shoulders, lumbar region, thighs and upper arm. ALEXANDER (*Deutsch. med. Wchnschr.*, 1924, 51, 300) considers treatment of this condition with extracts of single organs, such as the thyroid or ovary, illogical and unsatisfactory, and for a long time has used lipolysin (Dr. George Herring, Berlin) with good results. Lipolysin is a mixture of the extracts of the thyroid, hypophyseal, pancreatic and genital glands; lipolysin masculin, containing an extract of the testicle, and lipolysin feminin, an extract of the ovary. Lipolysin causes at first a marked diuresis and relief of the spastic constipation, which commonly is found in these cases. During the early part of the treatment the fluid intake should be diminished, and carbohydrates and fat restricted. The best diet is one containing an abundance of vegetables and meat. The most satisfactory results with the use of lipolysin were obtained when injections of the mixture were given every other day and two tablets by mouth on the intervening day. When twelve injections have been given the tablets are administered by mouth only unless there is an increase in weight or swelling of the tissues. A total of twenty-four to thirty injections and from one hundred and twenty to one hundred and fifty tablets may be given without danger. At the termination of the regular treatment two to three injections may be given before the menstrual periods to relieve the dysmenorrhea and prevent a recurrence of the pluriglandular insufficiency which may result from the menstrual disturbance.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

The Relation of Heredity to Diseases of Infancy and Childhood.
—HERRMAN (*Arch. Pediat.*, 1924, 41, 301) says that physicians have not given the subject of heredity the attention that it deserves. The remarkable progress in bacteriology is largely responsible for this neglect of the difference of the reaction of different individuals to the same external agents. It is important to detect unfavorable peculiarities and tendencies early in childhood in order that their further development may be prevented. The inheritance of physical and mental peculiarities apparently follow the same laws. Both are present in the same individual. For proper study of the laws of inheritance complete family histories and pedigree charts are essential. Tendencies and peculiarities, although on a hereditary basis and congenital, may not manifest themselves at birth, but may develop later when the indi-

vidual is called upon to bear an increased burden as a result of such causes as improper feeding, an unfavorable environment, infection or psychical shock. Inherited tendencies may manifest themselves in the appearance of one or more of a group of related conditions—in the the vulnerability of a certain organ or system, or in the appearance of congenital deformities. Good health and nutrition do not necessarily go hand in hand with resistance to the infectious diseases. The ability to develop active immunity appears to be distinct for each infectious disease, and it is probably on a hereditary basis. The ability to develop antitoxin in diphtheria acts as a dominant character. The germ plasm, although a part, is distinct from and, to a great extent, independent of the organism itself. The normal intact placenta acts as an effective barrier against the transmission of injurious substances to the fetus through the placental circulation. In time there is the best opportunity to study the relative importance of heredity and environment in the development of the human being. Acquired characteristics are not inherited. The environment cannot originate or create new qualities. The potentiality must be present. The environment may modify, hasten, retard or inhibit the development of latent qualities. Prenatal care of the mother, although of great value, has a definite limitation so far as the development of the fetus is concerned. Syphilis in the mother can be treated, disturbances of renal function can be detected, pelvic deformities can be noted, but certain fundamental defects, which have their origin in the germ plasma, cannot be influenced. At present only the worst kind of mating can be prevented by law. The best can be encouraged. A spread of the knowledge of the importance of the subject through educational propaganda is essential.

A Morphological and Quantitative Study of the Blood Corpuscles in the Newborn Period.—LIPPMAN (*Am. Jour. Dis. Child.*, 1924, 27, 473) found that the morphology of the blood of the newborn differs in many ways from that of the adult. His study was undertaken to fill a gap in the knowledge of newborn blood during the first forty-eight hours after birth. So many changes occur at this time that a careful analysis of the variations is essential. The forty-eight-hour period has been divided into eight parts, 30 cases being considered in each interval. Counts were made of the red blood cells, leukocytes and platelets. Differential studies included the examination of 500 cells in each smear. White counts and differential studies were again made at five days to secure a further check on the material. The red blood cells at birth average 5,200,000 per c.mm. During the first six hours the count rises to 5,600,000. Following this there is a drop to 5,400,000 at eighteen hours, after which the count remains at a fairly constant level until forty-eight hours after birth. The platelets at birth average in the counts 5,200,000 per c.mm. It drops to 170,000 during the first six hours. The decrease continues until eighteen hours after birth, and is followed by a slight increase. No changes from normal were observed in the platelet counts in icterus neonatorum. The total leukocyte count at birth average 16,600 per c.mm. At twelve hours it is 22,500, after which it gradually drops to 11,300 at forty-eight hours. At five days it has decreased to 9500. The differential counts

show wide variations. The averages present curves which are often quite different from those reported in the literature. One of the striking features observed was the marked changes which may take place within a very few hours. In one instance the white cell count jumped from 25,000 to 34,000, while the polymorphonuclear cells increased from 38 to 61 per cent within six hours. It is important in any differential blood study to determine the absolute cell counts as well as the percentages. The curves often differ from each other to a great extent. The polymorphonuclear neutrophils follow closely the total white cell count, and are primarily responsible for the leukocyte curve in the newborn period. The neutrophilic melamylocytes are very numerous in the newborn blood. Values as high as 43 per cent have been observed. Neutrophilic myelocytes are infrequent in newborn blood, but are most numerous during the first eighteen hours.

The Effect of Freezing on Diphtheria Toxin-antitoxin Mixtures.—ANDERSON and LEONARD (*Jour. Am. Med. Assn.*, 1924, 82, 1679) examined 15 lots of toxin-antitoxin mixtures containing three L+ doses of toxin, prepared with a highly refined globulin in which 0.3 per cent tricresol was used as a preservative. This showed no increase in toxicity after freezing. Eight lots of diphtheria toxin-antitoxin mixture, prepared with a highly refined globulin, containing one-tenth L+ dose of toxin, with 0.3 per cent tricresol used as preservative, developed no increase in toxicity after freezing. Mixtures of diphtheria toxin-antitoxin prepared as stated became on the average less toxic after freezing. Mixtures prepared with three L+ doses of toxin, with 0.3 per cent tricresol, and made with an antitoxin that had been concentrated without the use of heat, showed an increase in toxicity after freezing. Diphtheria toxin-antitoxin mixtures prepared with unconcentrated antitoxin, with three L+ doses of toxin, 0.3 per cent tricresol or 0.5 per cent phenol being used, increased in toxicity after freezing. Diphtheria toxin-antitoxin mixtures prepared with unconcentrated antitoxin, with three L+ doses of toxin, chlorbutanol or chloroform being used, or without preservative, showed no increase in toxicity after freezing. Diphtheria toxin, after freezing at -5°C . for forty-eight hours, showed a decrease in toxicity. In the mixtures prepared with unconcentrated antitoxin, containing three L+ doses of toxin, with tricresol as a preservative, and subsequently frozen, there became dissociated approximately twenty minimal lethal doses of toxin. This free toxin was neutralized by the addition of diphtheria antitoxin or the simultaneous administration of antitoxin, so that acute death was prevented. Paralysis and local reactions sometimes developed.

Wasting Disorders of Early Infancy.—PARSONS (*Lancet*, 1924, 1, 1793) points out that in infantile atrophy infants after thriving normally begin to lose weight for one or more causes, such as insufficient or unsuitable food, diarrhea and vomiting, infection, hygienic surroundings or prenatal influences or constitutional causes. Many of these children can, and do, absorb a larger amount of fat per 1 kg. of body weight than normal children usually do, but a high-fat dietary may cause fat indigestion, and with diarrhea, in whatever manner produced there is diminished fat absorption. Calcium absorption is

usually very good if a sufficient supply of fat and calcium is present in the food. Many of these children absorb more calcium per 1 kg. of body weight than normal children usually do, but in a poor-fat or calcium dietary the absorption is not good. There is present in many cases faulty salt metabolism, which may result in low retention values for calcium. Protein metabolism is also faulty. The absorption of protein is normal; protein indigestion is rare, and has only been seen where there has been a large protein intake over a considerable period of time. The metabolic disturbances are essentially abnormal salt metabolism and abnormal protein metabolism, resulting in poor retention values for mineral salts and nitrogen.

Acute Appendicitis in Children.—MÜLLER and RAVDIN (*Jour. Am. Med. Assn.*, 1924, 82, 1852) review the records of 58 patients, of whom 54 recovered and 4 died, a mortality of 6.8 per cent. There has been a marked decrease of the mortality rate in children in the past decade. This is more striking than the reduction in the mortality rate in adults. The lower mortality has been brought by early diagnosis and early reference to the surgeon for operative intervention. The mortality can be further reduced only by an earlier differentiation of these cases from the conditions that simulate it, such as pneumonia, pyelitis, Pott's disease, gastroenteritis, fecal impaction and intestinal obstruction. It is interesting to note that the low mortality rate existed in spite of the following complications: Twenty-eight cases, or 48.3 per cent, had peritoneal extension at the time of operation. Twelve of these, or 42.8 per cent, had local peritonitis, and 7, or 25 per cent, had generalized peritonitis. In 30 cases the inflammation was localized at the appendix; 29, or 50 per cent of the patients, were purged before operation. In nearly every case the purgation had been repeated. The administration of purgative before an absolute diagnosis has been established, has been the cause of more harm than any other factor connected with the disease. If it is necessary to obtain an evacuation of the bowel before a diagnosis has been established adequate results can be obtained by the use of an enema. One of the most important factors in establishing the diagnosis is a complete leukocyte count. In this series it was found to be almost constantly high.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

Unusual Toxemia of Pregnancy.—HEIDLER (*Monatschr. f. Geburtsh. u. Gynäk.*, 1923, 63, 249) describes the case of a woman, aged twenty-two years, who had the usual diseases of childhood and was brought to the hospital in her first pregnancy. On examination she was fairly

developed; there was no edema; the fundus of the uterus was four finger breadths beneath the tip of the sternum; a child presenting by the vertex, the head at the brim of the pelvis. The heart sounds could be heard distinctly and the pelvis was of average size. She had become unconscious at midnight preceding her admission. The patient's mother stated that several months before admission after a short period of unrest the patient had suddenly become unconscious with slight convulsive movements over the whole body, cyanosis and the expulsion of foam from the mouth. These attacks had recurred until she had twenty. A midwife was called, who sent her to the hospital, where she was admitted in an unconscious condition but otherwise not in a serious state. There were very slight disturbed motions, but deep stupor. From this the patient suddenly aroused and had to be restrained by the use of morphia; when the effect of the drug wore off she was again unruly, and complained of intense hunger and asked for food. This was followed by further unconsciousness and vomiting from which she recovered. The urine showed a faint trace of albumin and a few casts; the eyes were normal. The patient felt much better in a few days and was discharged from the hospital to her home. The diagnosis was made of intercurrent eclampsia and the patient strongly urged to report regularly to the clinic for observation; this she did not do. She went through the pregnancy without further complication and gave spontaneous birth in her home to a well-developed child, apparently healthy. Her second pregnancy ended with spontaneous abortion and her third in an abortion at six months, her fourth in normal labor at the hospital and in the fifth pregnancy she came under the observation of the writer. The patient remembered very little of the complications of her previous pregnancies, but during the present pregnancy she had several attacks of unconsciousness, from which she would suddenly recover. These attacks were without premonition, some occurring at night; mostly during the day. Some occurred while the patient was upon the street, and she was brought home in this condition. When in the non-pregnant condition she had nothing whatever of this sort. As pregnancy drew toward its close the attacks were less frequent, but an accurate history concerning them could not be obtained as no physician had ever seen her in one of the attacks. When the patient came under the observation of the writer she was well nourished, the skin was dry, the thyroid not enlarged, the face slightly reddened, the patient answered questions intelligently and was animated and there was no edema. Urine obtained by catheter was negative. A small quantity of urobilin was present. The blood showed 2,731,000 red cells; leukocytes, 5200 per c.mm. A Wassermann reaction was negative. A minute examination of the blood for thrombocytes and fibrinogen revealed nothing extraordinary. The neurological and psychological examination revealed no scar on the tongue; reaction to electricity normal; no evidence of hysteria and no signs of epilepsy. The patient's labor was spontaneous, with recovery of mother and child normal. To sum up the case, a woman aged twenty-two years, without hereditary history of nervous or other disease, in five pregnancies had during the first, attacks of unconsciousness, with very slight albuminuria; this pregnancy terminated in normal labor;

the following pregnancies showed the same phenomena and they developed so soon after the pregnancy occurred that their appearance led the patient to suspect that she was pregnant before any other symptom had appeared. There was absolutely no sign of any such condition when the patient was not pregnant. An effort was made to test the patient by injecting adrenalin, as it has been found that under certain diseased conditions of pregnancy, adrenalin produces an unusual reaction; in the case described no such reaction occurred; this was repeated with negative result. Pilocarpin was next tried, with negative result; to test the function of the liver milk was used, and an examination made for leukocytes with the usual result. Comparing this case with one reported by Curschmann, the suggestion of cortical epilepsy is made as the probable cause. In Curschmann's case there were Jacksonian attacks and hemiparesis from which the patient recovered.

Cerebral Symptoms Produced by the Toxemia of Pregnancy.—APEL (*Zentralbl. f. Gynäk.*, 1923, 4, 160) reports the case of a woman in her fourth pregnancy, aged twenty-six years, brought to the clinic alleged to have eclampsia. An accurate history could not be obtained, and her appearance suggested the somnolent condition which eclampsia often manifests between convulsions. It was stated that at twelve years of age she had measles severely, followed by paresis of the extremities, persisting for several days. She had otherwise been apparently healthy, of average intelligence and ability. When eighteen years old her first child was born, a year afterward a second without special complications, a third birth followed and 2 of the children perished—1 shortly after birth and 1 three weeks later from spondylitis. She had naturally been greatly disturbed by the loss of the children, but the present pregnancy had proceeded up to the time of admission without complications. She was taken suddenly during the night with a convulsive attack, after which she complained of headache and remained in bed for a day; she was then able to resume her housework, when two other convulsions followed and she was sent to the hospital. On examination she was well developed and vigorous, and the internal organs showed no pathological condition. The reflexes were practically normal, except the plantar reflex which was increased, while the reflex of the abdominal wall was absent. Variations in sensations could not be demonstrated. The tongue showed no injury; the pulse and temperature were normal. The systolic blood-pressure was 120 mm., mercury; the urine was normal. The size of the uterus indicated seven months' pregnancy. Heart sounds were heard. The cervix uteri admitted one finger and the cervix was not obliterated, but the membranes could be felt and showed no signs of pressure. During the examination the patient had an attack: The head was slowly turned to the left; both arms were extended then flexed and turned toward the left; the right arm and leg were then extended and clonic convulsion occurred. During the attack the muscle tone was relatively diminished; the mouth was widely open; the tongue was not bitten; both eyeballs turned sharply toward the left; the pupils reacted directly after the convulsion and at the end of the attack, which lasted half a minute, there was very little cyanosis and secretion of saliva.

The patient did not become comatose, and speedily became conscious. The attack was not typical of eclampsia and 0.4 gm. of luminal was given by intramuscular injection. These attacks returned and were uninfluenced by sedatives and narcotics. The urine remained normal; the vascular system showed no variation; the temperature rose to 99 to 100° F., and the same night a living male child was suddenly born, and the placenta expelled with very slight loss of blood. After the expulsion of the child the patient's condition remained practically the same; the attacks recurred and were not controlled by luminal and morphin. The condition of the nervous system was essentially the same and there was a slight facial paresis on the left side. An examination of the eyes showed a slight projection in the optic nerve on the right side. Convulsions then became very frequent, the left side of the body showing much more violent convulsions than the right. The pulse rose to 100; the temperature fell somewhat; the patient became comatose and was controlled somewhat by scopolamin. Abundant tracheal rales were present, the sputum was retained and the patient seemed in a very critical condition. The number of attacks had reached more than 100. On the following day after a succession of attacks in the early morning the patient was transferred to the neurological clinic, and after a brief period the attacks ceased and the patient was discharged. The writer is positive that this was not eclampsia of the usual form; that it was toxemia of pregnancy there can be no doubt and that it was accompanied by some cerebral lesion of a chronic and latent nature he considers also to be a most rational explanation. He quotes numerous authors who report anomalous cases of convulsions in parturient women, and among them the case of a woman who when two years old had been seriously ill with measles and thirteen years later developed epilepsy from cranial and cerebral irritation. Examination of the cranium by the roentgen-ray showed a deposit of calcareous matter in the cranial wall and the resulting condition of chronic irritation.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, MEDICAL SCHOOL, UNIVERSITY
OF PENNSYLVANIA, PHILADELPHIA.

Tests for Cure of Gonorrhea in Women.—In undertaking the treatment of gonorrhea in the female, it is important to know when it is safe to discharge the patient as cured, which is often a difficult thing to determine. According to ABRAHAM (*Lancet*, 1924, 206, 429), the

first criterion is that all clinical signs of the disease must have disappeared. By this is meant: (1) That there is no induration of Bartholin's glands, or sign of inflammation around their orifices; (2) that the urethra appears normal on inspection externally, palpation through the vagina, and urethroscopical examination; (3) that the paraurethral crypts, especially Skene's tubules, show no inflammatory signs; (4) that the vaginal introitus is normal in color, with no inflamed tags or crypts around it, and that pain is not complained of when a speculum is passed; (5) that the cervix appears normal, the secretion clear, and no erosion is present; (6) that the uterus and tubes, on bimanual examination, are apparently free from disease; and (7) that the anal orifice seems normal, and there are no signs of inflammation or discharge in the anal canal on passing a speculum. The second essential desideratum is that all bacteriological signs of disease should be absent. Evidence on this point can only be accepted if the following technic, and the precautions mentioned below are observed in making the examination: (1) Smears taken from the urethra by means of a sterile platinum loop inserted half an inch down, should be negative for pus cells and gonococci in a patient who has had a provocative injection of 1 cc of gonococcal proteose twenty-four hours previously. The urethra should be massaged gently forward before the loop is inserted, and the surgeon should assure himself that the patient has not passed urine for some hours before the examination; (2) the urine held for some hours before examination, should be clear, acid, free from albumin and contain no gonococci or pus, when the centrifuged deposit is examined under the microscope; (3) smears taken from the orifices of Bartholin's glands and from Skene's tubules should be negative; (4) smears taken from the cervix by means of a platinum loop should be negative for gonococci and pus, when taken before menstruation, just after menstruation has ceased and twenty-four hours after a provocative injection of 1 cc of gonococcal proteose; (5) smears taken from the anal canal should be negative for the gonococcus. The anus is a fruitful source of reinfection. Gonococci can often be found there when they are absent elsewhere in women. Nothing is said about attempting to grow the gonococcus from smears, because he believes the method is useless. In regard to the complement-fixation test, Abraham has found that in the acute stages of a urogenital infection the test is useless as a means of differentiating between a gonococcal and non-gonococcal infection, but if the infection has existed from two to six months, then a negative test indicates that the disease is non-gonococcal, in other words, the reaction is specific. If a positive test is present a year after all clinical and bacteriological symptoms have disappeared, it may be neglected for all practical purposes. In brief, in the early stages of gonorrhea, the test is not sufficiently powerful to diagnose the disease, in the middle stages it will differentiate between gonococcal and non-gonococcal disease, and in the convalescent stage it is too delicate for use as a practical sign of cure.

Roentgen Therapy of Benign Uterine Bleeding.—Basing his observations on the treatment of more than 500 cases of uterine fibroids and uterine bleeding not due to malignancy, WILLIAMS (*Am. Jour. Roentgenol.*, 1924, 11, 252) states that the cases in which this form of

therapy is indicated are as follows: (1) Fibroid tumors of the uterus, except the pedunculated submucous type, or those showing degeneration; (2) functional menorrhagia and metrorrhagia of adolescence; (3) menorrhagia and metrorrhagia without evidence of gross pathology and most commonly observed in the fourth decade; (4) menorrhagia and metrorrhagia due to metritis or endometritis of hypertrophic or polypoid nature. A contraindication for this treatment is infection, active or latent, in the pelvis. An old quiescent infection may be converted into an active process by radiation therapy. When there is some complicating lesion requiring surgery for relief, this form of treatment should be used only as an adjuvant, for instance, to check hemorrhage. From the foregoing observations it should be realized that a complete pelvic examination should be made by a competent diagnostician before instituting this treatment. About two years ago a new technic was developed which has been constantly used since that time. Instead of using multiple portals of entrance, the treatment is given through a single large one. Where there is a large tumor present, the portal is sufficiently large to include the entire tumor. A fibroid uterus the size of a five months' pregnancy will not be palpable above the symphysis and will be but little above normal size after four treatments. Larger tumors extending to the navel or above gradually diminish in size, the full effect of the treatment not being realized in less than one year. Radiation therapy controls hemorrhage in these cases through its effects on the ovaries and on the development of the Graafian follicles. There is some diversity of opinion as to whether the reduction in size of a fibroid uterus is due to the direct action of the rays on the tumor or whether it is secondary to the effect on the ovaries, it having been known for a long time that these tumors do diminish in size after the menopause. From the author's own experience, he believes that the reduction of the tumor is due to the direct action of the rays. If after roentgen-ray therapy, the patient complains of pain in the pelvis, especially if it be a unilateral pain, or develops fever or chills, the treatment should be discontinued. These symptoms indicate the presence of some infectious process in the pelvis which has been overlooked. A single treatment will probably not seriously activate a latent infection, but repeated treatments most certainly would do so.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO; TORONTO, CANADA,

AND

DE WAYNE G. RICHEY, B.S., M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY, UNIVERSITY OF PITTSBURGH; PITTSBURGH, PA.

A Medium for the Inhibition of Spreaders and the Differentiation of *B. coli* and *B. aërogenes*.—By adding 1/100000 of crystal violet to Levine's eosin methylene blue agar, SKINNER and MURRAY (*Proc. Soc.*

Exper. Biol. and Med., 1924, 21, 188) found that none of the 50 strains of spore-forming organisms (spreaders) developed in twenty-four hours and 21 developed only slightly in forty-eight hours, the remainder never growing. The *Bacillus coli* colonies were black or dark bluish-violet by transmitted or reflected light, with dark centers reaching to the edge or nearly so. They tended to a decided green metallic sheen. The *Bacillus aërogenes* colonies were pink or light lavender by reflected light, by transmitted light, dark centers not reaching more than half way to the edge. The colonies were sticky, showing a decided tendency to run together (in contradistinction to the *Bacillus coli* colonies). There was no metallic sheen. In checking unknown colonies procured from soil sewage, feces and polluted stream water with the Voges-Proskauer test, it was found that 94.4 per cent of *Bacillus coli* agreed by the two methods and that 93 per cent of the *Bacillus aërogenes* agreed.

Studies Concerning the Significance of Streptococcus Hemolyticus in Scarlet Fever.—Since *Streptococcus hemolyticus* is almost constantly present in the throats of individuals suffering from scarlet fever, and since this organism is the preponderant causative agent of such septic complications of the disease as otitis media, adenitis, interstitial nephritis, arthritis and septicemia, many have regarded streptococci as the etiological agent of the disease. Moreover, since the development of a technic for the differentiation of biological types of *Streptococcus hemolyticus* by Dochez, Avery and Lansfield, various investigators have found that the type of hemolytic streptococcus found in the throats of scarlet-fever patients is in general a specific type readily distinguishable from the types of *Streptococcus hemolyticus* causing other kinds of angina and septic conditions in general. Recently DOCHEZ (*Proc. Soc. Exper. Biol. and Med.*, 1924, 21, 184), assisted by SHERMAN, has been able to produce in guinea-pigs a condition resembling in its main features certain phenomena of scarlet fever by the injection of a scarlatinal type of *Streptococcus hemolyticus*. Being impressed by the similarity of the symptom-complex in guinea-pigs to human scarlet fever, the author immunized a horse. It has been found that the immunized horse serum will neutralize the rash locally on the skin in human cases of scarlet fever. This cutaneous blanching was more conspicuous than that obtained under similar circumstances from the use of convalescent scarlatinal serum. The authors state that "Such a sequence of observations undoubtedly again throws the balance of evidence in favor of *Streptococcus hemolyticus* as the causative agent of scarlet fever." They liken the disease to diphtheria, in that the principal localization of the infection is in the throat, where the organism produces a toxin which gives rise to the general symptoms and the rash. Furthermore, they suggest that the immunity in scarlet fever is probably antitoxic in character and the blanching represents the neutralization of the toxin *in situ*.

Reactions of the Urinary Bladder in Canine Anaphylaxis.—As an index to possible smooth muscle reactions, MANWARING, HOSEPIAN, ENRIGHT and PORTER (*Proc. Soc. Exper. Biol. and Med.*, 1924, 21, 284) studied the pressure changes in the urinary bladder during canine

anaphylactic shock, with parallel tracings of the changes in the arterial blood-pressure. The dogs were sensitized to horse serum according to Weil's method and were tested by intravenous injections of 0.5 to 2 cc horse serum per 1 kg. of body weight about twenty-one days after the final sensitizing dose. The intracystic pressure was recorded by means of a glass catheter, and the abdomen was opened to avoid error from changes in intra-abdominal pressure. In typical anaphylactic shock the arterial pressure fell precipitously to about 35 mm. Hg. by the end of forty-five seconds, gradually decreasing to about 25 mm. Hg. by the end of ninety seconds. Recovery usually began about the twelfth minute, the blood-pressure being restored to normal in from sixty to ninety minutes. During the first forty-five to seventy-five seconds the intracystic pressure showed no recordable change, after which time it gradually increased, usually reaching a maximum of from 25 to 50 mm. Hg. by the end of two and a half minutes and returned to normal by the seventh minute. "Assuming that the cystic reactions thus recorded are reliable, indices to smooth muscle reactions in other parts of the body," the authors concluded "That in typical canine anaphylactic shock the smooth muscle structures are not thrown into contraction until the shock is fully established, as determined by the fall in arterial blood-pressure. The smooth muscle reactions, therefore, apparently played no role in the initiation of the shock. They also apparently have little or no effect on the duration or severity of the shock as determined by the changes in arterial blood-pressure." In an instance of rapidly fatal canine anaphylaxis the observations were such as to suggest that smooth muscle reactions became the dominant factor during the later stages of the shock and were apparently the immediate cause of death. Even in this type of shock, however, the smooth muscle reactions apparently played no part in initiating the shock.

Attempts to Separate the Active Constituent of Ragweed Pollen.—As ragweed appears to be the chief cause of hay-fever in this country, BAUMAN, CHUDNOFF and MACKENZIE (*Proc. Soc. Exper. Biol. and Med.*, 1924, 21, 226) deemed it advisable to attempt to separate the substance in the pollen which is responsible for the sensitization of hay-fever patients. It was found that the active substance could be completely extracted from ragweed pollen with 3 per cent ammonia and that it could be quantitatively removed from the ammonia extract by precipitation with acetone. As prolonged dialysis of the ammonia extract against 5 per cent sodium chloride failed to remove the active substance, it was inferred that it was in the form of a large molecule or aggregate. The "globulin fraction" seemed to be the more active, even when dialyzed for a number of days in collodion sacs, and the authors hope that more data may be obtained by a study of the behavior of this fraction.

Recovery of *Bacillus Histolyticus* from Human Feces.—Having recently recovered a strain of *Bacillus histolyticus* from a sample of arable soil in California, HALL (*Proc. Soc. Exper. Biol. and Med.*, 1924, 21, 198) has been able to isolate another strain of the same organism from the stool of a healthy prisoner in San Quentin Prison. The spore formers were recovered after heating to 80° C. for twenty minutes, using

deep brain medium for the initial culture and deep agar for isolation of the anaërobes. The strain was morphologically and culturally typical and, though not refusing to grow on the surface of solid media, preferred anaërobic conditions. The microorganism was exceedingly virulent when injected into a guinea-pig's leg. The author states that the finding of *Bacillus histolyticus* in human feces, as well as in cultivated soil, establishes a certain amount of evidence to explain its occurrence in wounds where conditions are favorable for contamination with fecally polluted soil.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

An Immunizing Strain of the Virus of Poliomyelitis.—FLEXNER and AMOSS (*Jour. Exper. Med.*, 1924, 34, 625) present certain facts regarding the virus of poliomyelitis. They show that strains of the virus exist in nature, which under some circumstances induce paralytic and lesser effects in monkeys, the inclination of which is toward amelioration terminating in recovery, instead of, as had been observed in the past, intensification leading to death. This latter consideration may in time come to have practical significance. The qualities which distinguish the attenuated strain of the virus raise the question whether the mild grade of activity is an inherent property, or whether it is a product of the mild putrefactive changes taking place in the human tissues. No answer can be returned at present to this question, which, however, may not prove entirely beyond experimental determination. It has been ascertained by experimental tests that the modified form of poliomyelitis through which the inoculated monkeys pass, and from which they recover, leaves them protected against the action of a highly virulent strain of the virus of poliomyelitis. The mild or attenuated strain of the virus seems to be of a fixed degree of potency, having neither increased nor decreased perceptibly in the two years during which it has been under study. Unless the virus was modified by the putrefactive process occurring in the original human brain and cord, it is obvious that wide disparity exists between the effects induced by the strain in the human being from whom it was derived and the monkeys into which it was inoculated. The former shows very severe acute lesions in the spinal cord and medulla, to which the death is attributable; the latter shows relatively mild lesions from which recovery, either complete or nearly complete, tends to take place.

Investigations on the Control of Hookworm Disease. XXXII. Methods of Measuring Human Infestation.—CORT (*Am. Jour. Hyg.*, 1924, 4, 213) recommends certain modifications of administrative procedure in hookworm control work, which seem to be of far-reaching significance: (1) The use of the egg-counting technic in the examinations of preliminary surveys will give quantitative data that will make it possible to adequately plan control measures, and in certain areas will undoubtedly alter the viewpoint of the administrator in regard to the need of control work; (2) the use of the egg count, in evaluating treatment, will make possible the saving of the expense of routine reexaminations; (3) finally, as a yardstick to measure the results of the control measures, the use of the egg count will place the hookworm campaign on an entirely new scientific basis and make much easier its justification to legislative bodies and the public in general.

The Cause of Influenza.—The findings of Olitsky and Gates, with reference to *Bacterium pneumosintes* as the causative agent in influenza, have been more or less confirmed by Gordon, in England, and Lister, in South Africa. On the other hand, several investigators have obtained negative results, some of which have not been published. DETWEILER and HODGE (*Jour. Exper. Med.*, 1924, 39, 43) have studied the question in the epidemic experienced in Toronto during the past winter. They investigated 6 cases of epidemic influenza in various stages of the disease. They found suspicious cultures of bodies resembling *Bacterium pneumosintes* in 3 cases—twice from the lung filtrates of inoculated animals and once from the filtrate of nasopharyngeal washings direct. In these instances material was obtained within thirty-six hours of the acute onset, thus confirming the observations of Olitsky and Gates. Macroscopical and microscopical findings in the lungs of inoculated animals were uniformly negative.

Viscosity and Toxicity of Arsphenamin Solutions.—VOEGTLIN, JOHNSON and DYER (*U. S. Pub. Health Rpts.*, 1924, 37, 179) studied the relation of certain physico-chemical properties of solution of arsphenamin to the toxicity of the drug. It was shown that there is a relation between toxicity and viscosity, the higher the latter, the higher will the former be found. The handling of the drug determines largely the degree of viscosity; thus, on allowing solutions to stand for a short time there is a readjustment with a reduction of viscosity, and, in consequence, of toxicity. The studies have a bearing on the immediate so-called "nitritoid" reactions that may follow the administration of arsphenamin.

A Study of the Treatment and Prevention of Pellagra.—GOLDBERGER and TANNER (*U. S. Pub. Health. Rpts.*, 1924, 39, 87) emphasize again the importance of fresh meat and milk in the treatment of pellagra. Their summary is as follows: (1) Eight well-marked, though not very severe (mainly dermal), cases of pellagra were treated with fresh beef as the only known therapeutic element in the diet. (2) In all 8 cases clinical improvement following the inauguration of the beef treatment.

(3) In 4 of these cases the treatment with beef followed an unsuccessful period of treatment with gelatin, the contrast in results tending to emphasize, on the one hand, the inadequacy of gelatin, and, on the other, the therapeutic potency of fresh beef. (4) The preventive value of milk was tested by daily supplementing the basic diet of a group of 29 inmates of the Georgia State Sanitarium with approximately 40 fluid ounces (1200 gm.) of buttermilk. (5) None of these patients developed any evidence of pellagra at any time during the period of observation, which, for 25 of the group, lasted one year, although it is believed that without the buttermilk or equivalent supplement upward of 40 or 50 per cent of the group would have developed pellagra within a period of three to eight months. (6) Fresh meat and milk contain the essential pellagra-preventive factor or factors. (7) It is estimated that about 4 to 4½ ounces (125 gm.) of fresh beef (lean round steak) and not over about 40 fluid ounces (1200 gm.) of buttermilk will suffice to prevent pellagra in all but very exceptional instances. (8) Fresh butter (from cows largely pasture-fed) ingested daily in quantities averaging approximately 125 to 135 gm. (butter fat, 100 to 110 gm.) failed to prevent pellagra in several instances in which it was tried. (9) Cod-liver oil ingested daily in quantities averaging upward of 2 gm. per kilo of body weight failed to prevent pellagra in several instances in which it was tried. (10) The primary etiological dietary factor in pellagra is a faulty protein (amino-acid) mixture, a deficiency in some as yet unrecognized dietary complex (possibly a vitamin), or some combination of these.

Human Hypersensitiveness Induced by Very Small Amounts of Horse Serum.—HOOKER (*Jour. Immunol.*, 1924, 9, 7) states that following toxin-antitoxin injections a noteworthy proportion of human subjects became hypersensitive to horse serum, as shown by specific endermal reactions. He discusses the pertinence of this observation to serum therapy in general, and recommends that, in order to avert the widespread and disadvantageous influence which such induced hypersensitiveness is likely to exert upon the use of therapeutic horse sera, some other animal be chosen for the production of that antitoxin which is destined for use in toxin-antitoxin mixtures.

Notice to Contributors.—All communications intended for insertion in the Original Department of this JOURNAL are received only *with the distinct understanding that they are contributed exclusively to this JOURNAL.*

Contributions from abroad written in a foreign language, if on examination they are found desirable for this JOURNAL, will be translated at its expense.

A limited number of reprints in pamphlet form, if desired, will be furnished to authors, *providing the request for them be written on the manuscript.*

All communications should be addressed to—

DR. JOHN H. MUSSER, JR., 262 S. 21st Street, Philadelphia, Pa., U. S. A.

THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

SEPTEMBER, 1924

ORIGINAL ARTICLES.

THE CAUSE OF DEATH IN DIABETES MELLITUS.

BY REGINALD FITZ, M.D.,

AND

WM. P. MURPHY, M.D.,

BOSTON, MASS.

(From the Medical Clinic of the Peter Bent Brigham Hospital.)

Introduction. Insulin will probably change the clinical picture and course of diabetes to a very considerable extent. In order to contrast what may happen in the future with what has happened in the past, it is important to put on record all possible cases completely studied before insulin came into general use. With this idea in mind we have analyzed the records of all the cases of diabetes in the Peter Bent Brigham Hospital which have died in the hospital after entering the medical wards.

We have divided the cases into two groups. The first group contains those cases dying in the hospital before January 1, 1923 and the second comprises those cases dying during 1923. We have made this arbitrary division because we have become fairly familiar with the use of insulin during 1923 and thus have a year's experience with the new remedy to contrast with almost ten years' experience without it.

Diabetes from 1913 to 1923. From 1913, when the hospital first opened until January 1, 1923, the diagnosis of diabetes mellitus was made in 562 cases admitted to the medical wards. Of these, 64 died in the hospital.

One interesting fact brought out from study of the records is

that the mortality was not constant from year to year but showed a surprising variability. In order to make this clear, the number of new cases admitted each year was tabulated and the number of deaths occurring among them. The data is given in Table I.

TABLE I.—THE VARIABILITY OF DIABETIC MORTALITY.

Year.	New cases admitted.	New cases dying in hospital.	Mortality per 100 cases.
1913 and 1914	46	2	4
1915	60	7	12
1916	72	9	12
1917	70	4	6
1918	57	7	12
1919	47	3	6
1920	60	1	2
1921	64	6	9
1922	86	10	12
Total	562	49	9

The annual mortality for the new cases varied between 2 and 12 per cent with an average mortality of 9 per cent. It is important to bear in mind that such variability in the mortality of new diabetic cases treated in a general hospital from year to year is possible. The explanation probably lies in the fact that diabetes may be either a very mild or a severe form of disease. Any form of hospital treatment will appear to be accompanied by a low immediate mortality if a sufficient number of mild cases are treated. On the other hand, a small sequence of severe cases will exaggerate the inevitable mortality which accompanies any chronic disease requiring hospital care. On the whole, therefore, conclusions in regard to the value of treatment as it affects the hospital mortality of diabetes may be of dubious value.

Of the 64 fatal cases, 55 were able to date the onset of their disease with a fair degree of accuracy. Thus we estimated the duration of diabetes in these cases, arranging the results according to age at the time of death. The results are shown in Table II.

TABLE II.—THE DURATION OF DIABETES.

Age at death.	Total number of cases.	Total duration of diabetic life, years.	Average duration of diabetic life, years.	Shortest duration of diabetic life, years.	Longest duration of diabetic life, years.
61 to 80	12	97.7	8.1	0.1	16
51 to 60	12	68.2	5.7	0.2	15
41 to 50	10	37.5	3.7	0.1	8
21 to 40	14	15.3	1.1	0.1	4
Less than 21	7	6.3	0.9	0.1	2
Total series	55	225.0	4.1		

This table shows, strikingly, the well-known fact that diabetes tends to become less severe as the age at which symptoms are first

recognized becomes greater. On the other hand, it illustrates the fact that acute diabetes may develop in persons of almost any age so that increasing years do not necessarily preclude a severe form of the disease.

Of the 64 fatal cases, 58 (90 per cent), entered the hospital shortly before death and had not been treated previously as Peter Bent Brigham Hospital patients. On the other hand 8 of the fatal cases in this series were able to date the onset of their diabetic symptoms and were treated by the hospital at more than one entry for varying lengths of time before death. It is interesting to see how the effect of hospital instruction and subsequent follow-up care manifested itself in the duration of these patients' lives. The data is shown in Table III.

TABLE III.—THE EFFECT OF TREATMENT ON THE DURATION OF DIABETIC LIFE.

Peter Bent Brigham medical number.	Age at death.	Duration of diabetic symptoms before treatment, years.	Duration of life after treatment, years.	Total duration of diabetes, years.	Average duration of diabetic life for patient of same age (taken from Table II.) years.
20064	64	6.0	1.8	7.8	8.1
6792	59	3.0	2.2	5.2	5.7
16376	52	0.3	7.7	8.0	5.7
6343	49	0.7	3.4	4.1	3.7
15067	48	1.0	7.5	8.5	3.7
14721	27	0.2	3.6	3.8	1.1
13363	19	0.1	1.1	1.2	0.9
16886	13	0.7	0.8	1.5	0.9

All but 2 of the cases treated for any length of time by the Peter Bent Brigham Hospital had a longer diabetic life than the average case of comparable age which entered the hospital just before death. Thus the treatment given appeared of definite value in prolonging life.

Physicians who treat many diabetics recognize the importance of early treatment in the course of any given case and realize that the best therapeutic results by any method are usually obtained in those cases which are thoroughly treated as soon as possible after the onset of illness. The justification for this belief is well shown by Peter Bent Brigham Hospital Medical No. 14721 who entered the hospital on April 16, 1917. The patient was a young woman, aged twenty-three years, who developed diabetic symptoms two months before entry. She was followed by the Hospital Staff until her death nearly four years later, and during this interval re-entered the hospital several times. At each entry certain details of treatment were changed. From the records, however, we were able to estimate from Woodyatt's formula the total glucose tolerance attained at each entry, and thus have a fairly accurate picture of the course of the disease. The case is of particular value as a necropsy was performed, showing no gross anatomical changes except calcifi-

cation of the mesenteric lymph nodes. The essential findings to illustrate the course of the disease in this case are given in Table IV.

TABLE IV.—THE COURSE OF AN UNCOMPLICATED CASE OF DIABETES.

(Peter Bent Brigham Medical No. 14721. A woman 23 years old.
Diabetic symptoms of two months' duration.)

Date.	Weight, kg.	Systolic blood pressure.	Glucose tolerance, gm.	Comment.
April 16, 1917 . . .	51.2	130	129	
Sept. 10, 1918 . . .	46.0	120	152	
Oct. 8, 1919 . . .	48.0	125	199	Before this entry patient gave up her diabetic diet.
Mar. 12, 1920 . . .	42.6	107	131	Before this entry patient gave up her diabetic diet and had an acute respiratory infection.
Nov. 4, 1920 . . .	39.0	104	...	Before this entry patient gave up her diabetic diet. Death in coma.

For almost two years and a half there was but little loss of weight, no fall in blood-pressure and an apparent gain in tolerance. After this experience with diabetic dieting the patient apparently became discouraged although she appeared to be doing well, and gave up taking care of herself. Then there followed a precipitous loss of weight, fall in blood-pressure, fall in tolerance and final death in coma.

Such an initial two-and-a-half-year record in a case treated shortly after the onset of symptoms is not unusual even in the youngest people. One must remember this fact in discussing the effect on tolerance of any specific form of treatment. For instance, it is reasonable to assume that in this particular case any restricted calory diet with a gram or less of protein per kilogram of body weight, whether it contained a high carbohydrate low-fat mixture or a low carbohydrate high-fat mixture would have been followed by an apparently increased tolerance and symptomatic improvement if given to the patient at any time during the first two and a half years of her diabetic life. This case serves as an example to illustrate how careful one must be in drawing conclusions, especially with insulin, in regard to the effect of treatment on tolerance. Cases will have to be studied for a long time in a most critical fashion before any accurate knowledge on the matter can be obtained.

Of the 64 fatal cases in the entire series, 37 were examined pathologically and thus the true cause of death is known. There were 4 coma cases (11 per cent) which showed no particular gross anatomical changes and in which the patients appeared to die from what may be called uncomplicated diabetic coma. There were 14 cases (38 per cent) which, with or without coma, had an obvious sepsis or a terminating acute infection. There were 7 cases of active pulmonary tuberculosis (19 per cent). There were 3 cases (8 per

cent) with unusual complications such as hypernephroma in 1 case, hemachromatosis in 1 case and lymphatic leukemia in 1 case. There were 9 cases (24 per cent) with cardiovascular complications including gangrene or nephritis. In other words, uncomplicated diabetic coma was a rare cause of death, while coma combined with infection was common; active pulmonary tuberculosis caused nearly as many deaths as did cardiovascular disease. One interesting observation brought out from the analysis of the autopsied cases was that diabetic coma, on the whole, was the common cause of death in the young people; pulmonary tuberculosis also tended to be a cause of death in this group as it occurred in five instances in people under forty and only twice in older persons; sepsis or a terminating infection of any sort occurred in diabetics of all ages; the cardiovascular or renal complications and gangrene were reserved for the elderly patients.

Three other interesting points came up in this study: Anemia as judged by the red blood cell count was very rarely seen. Leukocytosis shortly before death was common. Syphilis, as revealed by a positive serum Wassermann test or by gross anatomical evidence, was unusual.

Red-blood counts were made in 33 cases, and in only 7 was the count below 4,000,000. One of these cases had septicemia, 1 had hemachromatosis, 2 had advanced chronic nephritis with a zero phthalein excretion, 1 had tuberculous bronchopneumonia, 1 developed anemia rapidly after an amputation of the leg for gangrene, and 1 was supposed to have cirrhosis of the liver and syphilis. In each instance, therefore, significant anemia was of definite prognostic significance and pointed to a serious complication.

White blood counts were made in 60 cases shortly before death. In 34 cases the white count was more than 16,000 and in only 10 cases was it less than 10,000. The white blood counts in the cases of severe acidosis are shown in Table V.

Of the 28 cases only 9 had a white blood count of less than 15,000 and only 3 of less than 10,000. Furthermore leukocytosis was often found in the absence of any demonstrable infection. It is thus apparent that leukocytosis tends to accompany severe diabetic acidosis. This fact may be of clinical significance. Leukocytosis may well be due to the concentrated blood so often found in diabetic acidosis due to anhydremia, or it may be due to infection without signs or symptoms which an acidotic diabetic patient acquires just before death. Therefore patients with acidosis must be given plenty of fluid and must be protected from exposure to infection in every possible way.

Blood Wassermann tests were made in 50 cases and were negative in 45. One case with a positive test was found at necropsy to have lobar pneumonia of the left lower lobe, general anasarca, chronic adhesive pleurisy of both lungs, chronic adhesive perihepatitis,

adhesive pericholecystitis, edema of the pancreas with connective-tissue increase and atrophy of the islands of Langerhans. A second necropsied case with a positive test was found to have suppuration of the ethmoidal cells and middle ear with acute meningitis, healed bilateral pulmonary tuberculosis and chronic fibrous pleuritis.

TABLE V.—THE WHITE BLOOD COUNT IN CASES OF SEVERE DIABETIC ACIDOSIS.

Peter Bent Brigham medical No.	White blood count.	Plasma bicar- bonate or alveo- lar CO ₂ in mm. of mercury.	Clinical cause of death.	Necropsy findings.
19254	20,800	20.2	Acidosis, septicemia	Generalized sepsis.
16732	4,900	10.2	Acidosis, arterio- sclerosis	Arteriosclerosis. Acute pericarditis.
2862	4,600	19.0	Acidosis,	
19627	12,100	9.6	Acidosis, broncho- pneumonia	Bronchopneumonia.
3907	19,200	8.9	Acidosis	
15067	14,500	Acidosis, chronic myocarditis	
7541	23,000	16.0	Acidosis	
16866	34,700	14.6	Acidosis, acute peri- carditis	Acute pericarditis.
5798	31,600	Acidosis	
17049	16,300	13.3	Acidosis, pulmonary tuberculosis	Pulmonary tubercu- losis.
6134	44,000	Acidosis	
15975	7,200	14.0	Acidosis	
2932	10,900	Acidosis	
20064	40,400	8.1	Acidosis, broncho- pneumonia	Bronchopneumonia.
13271	13,000	17.1	Acidosis	Bronchopneumonia.
20128	26,000	Acidosis, sepsis	Bronchopneumonia, sepsis.
11330	10,800	14.0	Acidosis	
18002	21,250	Acidosis, broncho- pneumonia	Bronchopneumonia.
14721	35,000	10.9	Acidosis	No infection demon- strable.
19653	14,300	Acidosis	No infection demon- strable.
12189	16,700	11.0	Acidosis	No infection demon- strable.
19183	13,600	Acidosis	
9979	41,800	10.0	Acidosis	
373	29,000	Acidosis	
9993	22,200	12.6	Acidosis, infection	
3283	18,000	20.0	Acidosis	Sepsis.
3224	44,800	12.7	Acidosis	No infection demon- strable.
3166	26,500	Acidosis	

The other cases with positive reactions were not autopsied. One apparently died of pneumonia, 1, a child of seven, in coma, and 1, following an amputation of the leg for gangrene, of arteriosclerosis with chronic myocarditis and heart failure. The large number of fatal cases with negative Wassermann reactions and without patho-

logical evidence of syphilis suggests that luetic diabetes is a very rare condition if it exists at all.

Taking the clinical records of the 64 fatal cases of diabetes as a whole there were 4 common causes of death. These causes were coma with or without a terminal infection, sepsis, cardiovascular or renal disease including gangrene, and pulmonary tuberculosis. Coma and pulmonary tuberculosis tended to occur in the younger patients, gangrene, cardiovascular or renal disease in the older patients, and sepsis in patients of any age. Additional facts of interest brought out in the review were that the annual mortality of new cases treated varied so much from year to year as to make conclusions with regard to the value of treatment as it affected the hospital mortality of diabetes during any one year of but little value. Diabetes became less severe as the age at which symptoms were recognized became greater although increasing years did not necessarily guarantee mild diabetes. Hospital treatment was of value in prolonging life. Coma, uncomplicated by a terminal infection, was rarely seen. Significant anemia was of prognostic significance as it pointed to a serious complication. Leukocytosis was the rule in severe acidosis. Syphilitic diabetes was a rare condition, if it existed at all.

Diabetes during 1923. During 1923, 124 new cases of diabetes were admitted to the medical wards of the hospital. Eight of these cases died, making the mortality for the year 6.5 per cent. In addition, 2 cases which had first entered the hospital previous to 1923 died, so that we have had 10 hospital deaths in all.

As has already been stated, the annual mortality of our new cases in the past has varied so much from year to year as to make conclusions in regard to the value of treatment as it affected the mortality during any one year of dubious value. Nevertheless it is interesting that the first year of insulin should have been accompanied by a mortality among the new cases appreciably lower than the average mortality during the ten previous years and only half as great as that of 1922.

Of the 8 fatal new diabetic cases in 1923, 4 were necropsied. The first patient, a girl, aged twenty-two years, died in typical coma. She had been receiving insulin for six weeks previous to her death and had been progressing satisfactorily until she became ill with a sore throat. Almost immediately glycosuria and acidosis developed. She was brought to the hospital in an ambulance from a city twelve miles away after being comatose for twelve hours and died shortly after entry. Necropsy showed a streptococcus septicemia.

The second patient was a man, aged fifty-two years, who also died in coma. His diabetic history was of about a year's duration although there had never been progressive loss of weight, polyuria or polydipsia. He was brought to the hospital after being unconscious for nearly twenty-four hours and he died shortly after admission. Necropsy was limited to an examination of the kidneys and

pancreas. These organs gave evidence of diabetes and a moderate degree of chronic nephritis.

The blood-sugar concentration at entry in this case was 0.84 per cent, the blood-urea nitrogen was 61 mg. per 100 cc of blood and the plasma CO_2 was 34.2 volumes per cent. The urine contained albumin, 5 per cent of sugar, and very little acetone or diacetic acid. The sediment contained rare leukocytes and occasional hyaline casts.

The case appears on our records as one of diabetes mellitus and diabetic acidosis. It is a question, however, whether the diagnosis of diabetic coma is justified in a case of diabetes not receiving alkali which dies comatose with no more marked a degree of acidosis than one producing an alkali reserve of 34 volumes per cent. The limited necropsy in this case did not help to clear up the diagnosis.

The third patient was a woman, eighty-five years of age. She had been under treatment for diabetes during the five years before her death and came to the hospital because of an acute respiratory infection. She died shortly after admission without evidence of acidosis. Necropsy showed that the chief cause of death was bilateral pneumonia. There was also a generalized arteriosclerosis.

The fourth case, a woman, aged fifty-two years, was known to have had diabetes for three years before her death. She had been feeling well until the day before admission when she suddenly became irrational, later drowsy and finally unconscious. Physical examination showed a marked degree of arteriosclerosis and a systolic blood-pressure of 200. No definite paralysis was noticed but the biceps and triceps reflexes were hyperactive on the left, there was spasticity of the left arm and a positive Babinski reflex on the left foot. The blood-sugar concentration was 0.32 per cent, the alkali reserve was 51 volumes per cent, and the blood-urea nitrogen was 22 mg. per 100 cc of blood. A single specimen of urine contained 2.8 per cent of sugar and a trace of albumin; the sediment contained numerous hyaline and finely granular casts. In view of the lack of acidosis and the presence of definite neurological signs the clinical diagnosis was made of diabetes mellitus, arteriosclerosis and intracranial hemorrhage. The patient died within a few hours. Necropsy showed generalized arteriosclerosis and marked coronary sclerosis. Permission to examine the head was not obtained.

Of the 4 fatal cases which were not necropsied 1, a woman, aged thirty years, died in coma after having had diabetic symptoms for a year. She became unconscious twenty-four hours before coming to the hospital and died a few minutes after entry. The second case was a woman, aged sixty-one years, who entered the hospital with a badly decompensated heart. She had no symptoms of diabetes but her urine contained 2.4 per cent of sugar and her blood-sugar concentration was 0.30 per cent. She died a few days after admission with signs of cardiac failure and with an alkali reserve of 46.2 volumes per cent. The third was a woman, aged seventy-six years,

known to have had diabetes for at least a year, and a carcinoma of the breast for a somewhat longer period. She entered the hospital with signs of a diffuse bronchopneumonia and died a few days later without any clinical manifestations of coma. The fourth case was a man, aged sixty-one years, who developed diabetic symptoms fourteen years previously and an intra-abdominal cancer about one year previously. He died about two weeks after entry without clinical manifestations of acidosis.

The two fatal cases of the 1923 series which entered the hospital for the first time previous to 1923, both died of heart failure. The first was a woman, aged sixty-two years, who entered the hospital in 1917, when, in addition to diabetes, she was found to have cardiac hypertrophy with dilation of the aortic arch and hypertension. There were no characteristic symptoms of diabetes, the glycosuria being found on routine analysis. After discharge she got along comfortably for five years when she became disturbed by increasing dyspnea and palpitation. She died a cardiac death without signs of acidosis although the urine contained sugar and the blood-sugar concentration was 0.32 per cent. Necropsy showed marked arteriosclerosis with hypertrophy and dilatation of the heart, and an aneurysm of the innominate artery.

The second case was a woman, aged sixty years, entering the hospital for diabetes in 1920. She was unable to date the onset of her illness with any accuracy, but was discharged in good condition on a liberal diet. She remained comfortable for two years when she suddenly experienced a severe cramping pain over the chest, neck and in both arms. On this account she made a second visit to the hospital, and in addition to diabetes was considered to have angina pectoris. Finally she entered for a third time in January, 1923, again having been comfortable until a recent sudden attack of precordial pain. She died a few days later without evidence of acidosis, the clinical cause of death being diabetes complicated by angina pectoris with a terminal infarct of the heart. Necropsy was not permitted.¹

¹ Dr. Joslin has suggested that the hospitals of Boston establish the precedent of publishing all fatal cases of diabetes which occurred during the past year. In order to coöperate in this plan we are appending the 3 fatal diabetic cases which entered and died on the surgical wards of this hospital. The first was a woman, aged seventy-six years, with diabetes of eight years' duration. In addition she had physical signs of arteriosclerosis and myocarditis. She entered the hospital for a fractured hip and died without acidosis or coma, a few days later. The second case was a man, aged sixty-four years, who entered the hospital on March 21 with a gangrenous foot. Sugar was found in his urine; there was no diabetic history. On April 6 the patient had a mid-thigh amputation from which he made a normal recovery. On May 7 he developed erysipelas of the face from which he recovered. On May 26 (nine weeks after entry) he developed femoral phlebitis which was followed by death, June 1. The third case was a woman, aged sixty years, who entered the hospital with cholecystitis. There was no history of diabetes. A cholecystectomy and choledochostomy for cholelithiasis was performed under ether. After the operation the patient sank rapidly and died within twenty-four hours. A sample of urine obtained after the operation contained 2.6 per cent of sugar. The record does not make clear whether or not there was glycosuria before operation.

On the whole, then, during 1923 the causes of death in our diabetic patients have been much as in previous years: Our patients died of coma, sepsis, cardiovascular disease or its complications, and malignant disease. We have been fortunate in having no hospital deaths from tuberculosis.

Lessons to be Learned from Fatal Cases of Diabetes. Joslin has pointed out that there are always practical lessons to be learned from a study of fatal cases of diabetes. Our cases seem to us to give the following information: In the first place, the treatment of coma is of utmost importance; therefore a good understanding of this condition is essential. As has been shown from our records, diabetic coma is primarily a cause of death in young people; moreover almost all comatose diabetics have a complicating infection which may well play a part in causing death. In view of these facts it is extremely important to prevent the development of coma by proper supervision of cases, to make the diagnosis of coma as early as possible, and finally, if coma does develop, to safeguard the patient from infection in every possible way.

The prevention of coma is largely a matter of education. All diabetic patients, and especially young patients, must be taught to keep their urines sugar-free, to balance their diets so that acetone bodies are not formed and to recognize the possible significance of even very minor ailments. Moreover they must learn when to call upon a doctor, and that if they feel unaccountably ill, bed, an enema, plenty of water to drink and a diet of orange-juice and gruel are the routine orders until the doctor assumes the responsibility.

The diagnosis of coma is a medical problem. It is important to remember that it is not easy to make the diagnosis in every case, witness one of ours in which the diagnosis remains uncertain despite a careful physical examination, chemical studies of blood and urine and a pathological examination of the pancreas and kidneys. However, there are certain physical signs and symptoms which occur fairly constantly and which justify emphasis. Diabetic coma is almost always accompanied by a subnormal temperature, a rapid soft pulse of low tension, a desiccated skin, soft eyeballs and an abnormal type of respiration varying from the slightest hyperpnea to most outspoken air-hunger. No patient in diabetic coma has a urine which does not contain sugar; albumin and showers of casts are frequently found. Acetone and diacetic acid may both be absent although both acids are usually present in large amounts. A well-trained nose can often detect the fruity acetone breath. Many cases seem to develop acidosis acutely with such initial symptoms as nausea, vomiting, abdominal cramps, restlessness and finally air-hunger. An antecedent history of diabetes is not necessary. Finally, most people are not introspective and all cannot state the onset of their illness with any accuracy: Many mothers do not know whether their comatose child has lost weight recently,

has been excessively hungry or thirsty, or even whether he has had a normal bowel movement in the last two or three days. Therefore, one must always exclude diabetic coma by urinalysis in a patient presenting any of the clinical signs of acidosis.

If diabetic coma does develop, the patient must be safe-guarded from infection in every possible way and given insulin. The patient must be kept in bed and must be kept warm; he should be given an enema at once; and plenty of fluid by mouth or rectum. If the stomach is not upset, a diet of orange-juice and gruel is satisfactory until the insulin arrives. Comatose cases often require considerably more insulin than other cases, therefore the drug must be given in relatively large amounts. It is safer for the patient to have a messenger bring insulin from the hospital rather than for the patient to go to the hospital for treatment and develop a fatal septicemia on the way by getting chilled and shaken up in an ambulance, especially because the home treatment of coma with insulin is perfectly safe and requires no more laboratory equipment than some Benedict's solution, a medicine dropper and a test-tube. After the emergency is over, the case can be hospitalized, if necessary, for purposes of education.

Sepsis is in many cases preventable through education. Diabetics must be taught to take care of themselves in every reasonable way. They must be told the possible significance of acute respiratory diseases, of intestinal infections, of skin infections, of chronic dental and tonsillar infections; they must learn to protect themselves from overexposure to cold and dampness, from overwork and worry. Finally, they must learn that infections of any sort invariably lower tolerance and that repeated minor infections can make a mild diabetic rapidly develop into one of great severity.

Cardiovascular or renal disease including gangrene often cause death in diabetes. Unfortunately cardiovascular and renal disease are very common in people past the middle period of life. Fortunately diabetes in this type of individual is usually mild, the patients are often obese and a low-protein low-calory diabetic diet is as good for the one disease as for the other. A mistake which we personally have been guilty of in the treatment of this type of case, however, is to discover the existence of diabetes through a routine urine analysis, thus have our attention focussed upon the blood or urine sugar, and as a result disregard the coexistence of what was a much more serious heart or kidney disturbance. In protecting this particular sort of case, therefore, one must remember the importance of diet for glycosuria, rest and digitalis for heart disease, limitation of fluid and salt intake for kidney disease, and above all the necessity of a systematic plan of life with prescribed diet, rest, exercise, and medication, and a due consideration of all the factors in this combination of diseases.

Gangrene is so common and so unnecessary in diabetics that as

Joslin has inferred, we should coöperate to organize an antigangrene campaign. Dr. Joslin's rules for care of the feet as a means for the prevention and treatment of this complication are inserted as being of the greatest practical value. We believe they should be enforced in all hospitals where diabetics are treated.

Joslin's Rules for the Treatment of the Feet in Diabetes. *General Hygiene.* 1. Wash the feet daily with soap and water. Dry them thoroughly, especially between the toes.

2. When the feet are thoroughly dry, rub them well with hydrous lanolin, as often as is necessary to keep the skin soft, supple and free from scales and dryness. If the nails are brittle and dry, soften them by soaking them in warm water a half hour each night and apply lanolin generously under and about the nails. Then bandage the feet loosely. The nails should be cleaned with orange-wood sticks. Cut the nails straight across and avoid injury to the toes.

3. Wear shoes which do not bind or rub. Wear new shoes one-half hour only on the first day and increase one hour daily.

Treatment of Abrasions. 1. In the diabetic, insignificant injuries may result very seriously, therefore proper first-aid treatment of any abrasion is of the utmost importance.

2. Thorough cleanliness with soap and water is necessary.

3. Strong irritating antiseptics such as sulphonaphthol and iodine are to be avoided.

4. The lesion should be covered with lanolin on sterile gauze under a slight bandage. Sterile gauze in small packages can be purchased at drug stores.

5. Avoid using the foot as much as possible until the wound is healed.

6. The patient must consult a doctor for any infection.

Treatment of Corns and Callosities. 1. Wear shoes which cause no pressure.

2. Soak the affected foot in warm, soapy water. Dry and rub or file off any dead skin. Then paint the corn with the following mixture: Salicylic acid, 1 dram, collodion, 1 ounce. Repeat the procedure for four nights, then, after soaking the foot in warm water, the corn will come off easily.

3. Do not cut corns or callosities.

4. Wear a pad to distribute pressure, if necessary.

Circulatory Aids. 1. Prescribed exercise.

2. Avoid sudden changes in temperature.

3. If the feet are subject to chilblains, wash them daily in warm water, dry them carefully and powder them lightly with borated talcum powder. Wear woolen stockings and avoid extremes of temperature.

4. Massage with lanolin.

5. Buerger's gravity—hyperemia method for bed-patients.

Conditions Requiring Attention in Diabetic Feet. 1. Cold feet.

2. Dry, scaling, atrophic skin.
3. Thick, dry, brittle nails.
4. Corns and callosities.
5. Cramps.
6. Stiff or limited joints.
7. Discoloration with red or bluish areas.
8. Clammy, moist skin.

Pulmonary tuberculosis judging by our necropsy material is fairly common. Out of about 1000 postmortem examinations in this hospital, active pulmonary tuberculosis was found in approximately 6 per cent; out of 42 diabetic necropsies active pulmonary tuberculosis was found in 16 per cent. Therefore active tuberculosis proved to be more than twice as common among the diabetics as among the patients as a whole. Since insulin appears to offer the tuberculous diabetic the same chance of recovery as would exist were the tuberculosis not complicated by diabetes, vigorous treatment for both conditions should be followed out in all cases.

The chief difficulty in this combination of diseases rests in diagnosis: Pulmonary tuberculosis is easily masked by diabetes and may be completely overlooked on ordinary physical examination. We believe that all diabetics, and specially those under forty years of age, should have routine roentgen-ray examination of the chest to exclude any pulmonary disorder. The necessity for this procedure will be made plain in a subsequent review of our tuberculous cases.

Conclusion. On the whole, insulin opens up so many new possibilities for the future treatment of diabetes that we believe it more important than ever to learn as much as possible from well-studied fatal cases. Therefore, we have presented this review of the cases of the medical clinic of the Peter Bent Brigham Hospital.

This study has justified the following conclusions: There were 4 common causes of death in the cases of this series and they represent the common causes of death in diabetes described by other authors. These causes are: Coma, sepsis, cardiovascular disease including gangrene, and pulmonary tuberculosis. Many diabetic deaths can be prevented and many diabetic lives can be happily prolonged if these causes are generally recognized and prevented or treated in their early development. A serious effort should be made through education to protect diabetic patients from the dangers—of coma, sepsis, and gangrene. Diabetic coma should be recognized at the time of its onset and treated before a terminal infection develops. Diabetics with cardiovascular and renal disorders should be as systematically treated for diseases of the heart, kidney or arteries as for diabetes. Pulmonary tuberculosis complicating diabetes should be discovered before it becomes hopelessly advanced, and both diseases when coexistent should be treated hopefully and vigorously.

THE OCCURRENCE OF HERPES ZOSTER IN HODGKIN'S DISEASE.*

BY HENRY K. PANCOAST, M.D.,

PROFESSOR OF ROENTGENOLOGY, UNIVERSITY OF PENNSYLVANIA,

AND

EUGENE P. PENDERGRASS, M.D.,

PHILADELPHIA.

THE occurrence of herpetiform eruptions in Hodgkin's disease is a rare condition, but it does occur more frequently than is generally recognized or taught. In reviewing the literature on Hodgkin's disease, the authors were unable to find a single instance in which mention was made of the occurrence of herpes zoster in the disease or as one of the skin complications.

After reviewing some of the literature concerning herpes zoster, we found one illustration¹ where herpes occurred in connection with Hodgkin's disease, but no other record of the case was reported. However, there were several reports of cases of malignancy which were complicated by herpes zoster during the course of the disease. It seems wise, therefore, to review some of the theories of the causes of herpes zoster in connection with this report.

In 1864, Mitchell, Morehouse and Keen² showed that irritation and not section of a nerve was the cause of zoster and similar eruptions. Later it was shown that compression by tumors, etc., might result in zoster along the distribution of the implicated nerve.

The simplest and most plausible theory of the production of zoster, and one, indeed, which must account for a certain number of cases, is that of propagated neuritis. This supposes that zoster is simply the result of an inflammatory irritation transmitted by continuity of tissue from a nerve twig, or branch, to the cutaneous elements among which it is distributed.

Cancer, otherwise than through the direct influence of pressure from the new growth, has been suggested as a cause of zoster. Cassière,³ in a case of femoro-cutaneous zoster following cancer of the uterus, found parenchymatous neuritis of the nerve involved. There was no cancerous infiltration of the nerve, and Cassière attributed the neuritis to the local and direct action of cancer toxins. One of Dr. Curtin's cases was also connected with cancer of the esophagus.

Head and Campbell,⁴ in a recent and extremely elaborate paper, give a large number of facts regarding the origin and distribution of zoster. These investigators have been able to map out the affected areas in zoster and have subsequently examined the spinal cord

* Presented before the Pathological Society of Philadelphia, May. 10, 1923.

and nerves implicated. They find inflammatory and destructive changes in the posterior ganglia of the cord and in the Gasserian ganglion, and degeneration in the nerves leading to the skin. In mild cases the effects of these changes gradually pass away, but in severe cases the nerve fibers that have degenerated are replaced by fibrous tissue, and whole bundles of the nerves may be sclerosed. Head and Campbell conclude that some agent, the nature of which we are ignorant, chooses the substance of the posterior root ganglion for its selected activity, producing profound inflammatory changes. These destructive changes in the ganglion give rise to irritation of its nerve elements, and to this irritation is due the eruption on the skin.

Case 14 in the series reported by Head and Campbell⁴ was a male, aged forty years, who seventeen days before death had a severe herpetic eruption over the 4th dorsal area. At the postmortem examination a mass of glands in the posterior mediastinum was profoundly affected by new growth passing in along the nerve sheaths through the foramina. The 4th dorsal ganglion was in the midst of lymphosarcoma tissue.

They also state, "It is well known that when the secondary deposits of malignant disease attack the spinal column the pain produced becomes intense. It is, however, less a matter of common knowledge than an eruption indistinguishable from that of zoster may also make its appearance. Charcot and Cutard gave a very insufficient report of such a case in 1865, but we can find but one other paper dealing with this subject, Riesel."

Hall¹⁶ in discussing the complications of new growths within the chest states that herpes zoster occasionally occurs along the nerve compressed by a new growth.

Thus one can readily observe that zoster does occur in patients having new growths, and although there are only a few reports on record, there are probably a number of other cases that have not been reported. Then too, most of the malignant cases are ambulatory, and one often does not see them except at long intervals, thus missing an acute attack of a condition such as zoster. There are recorded below 4 such cases occurring in Hodgkin's disease and 1 case of herpes zoster occurring in sarcoma of both ovaries. We feel that we have seen several times this number but due to incompleteness of our records, we are only able to report 5 definite cases.

Case Reports.—CASE I.—M. C., a female, aged twenty-seven years, married, was admitted to the University Hospital January 25, 1921, with the diagnosis of Hodgkin's disease.

H. P. I. In March, 1920, the patient had a sore throat and was in bed for a week. Two days later a lump developed on the left side of the neck, which slowly grew larger to the size of a hen's egg. Within a few months, involvement of the left epitrochlear, left

axillary, left preauricular and inguinal nodes became noticeable. The size of the glands varied from time to time. Since the beginning of the disease the patient has had a severe pruritus. At times she had fever and perspired freely. The glands gradually increased in size since first noticed.

Physical Examination. The skin was dark and showed numerous scratch marks. There was a general adenopathy especially in the axillæ, neck and groins, the glandular masses under the arms being about the size of an orange. The spleen was palpated and extended about 6 cm. below the costal margin. The inguinal adenopathy was more marked on the right side, the glands being about the size of walnuts. The blood counts were as follows: Red blood cells, 3,190,000; white blood cells, 32,000; hemoglobin, 55 per cent; differential polymorphonuclears, 87.5 per cent; lymphocytes, 8.5 per cent; large mononuclears 2 per cent; transitionals 1.5 per cent; myelocytes 0.5 per cent. The patient's temperature was elevated daily. The blood Wassermann test was negative. A pathological examination made by Dr. Fox revealed Hodgkin's disease. Roentgen-ray treatment was commenced and the patient received a general radiation over the body from February 11, 1920 to June 10, 1921. On July 25, 1921, the patient came in complaining of considerable pain in the right kidney region which was treated by roentgen-ray and radium with a temporary improvement. However, on October 26, 1921, the patient returned complaining of the same pain and shortly after developed a typical lumbar zoster of the hemorrhagic variety. The patient was again treated but without any beneficial results and later died.

Summary. A typical case of Hodgkin's disease with skin manifestations of herpes zoster late in the course of the disease at which time there were definitely enlarged glands palpable in the kidney region on the right side.

CASE II.—P. B., a female, aged ten years, was admitted to the University Hospital November 30, 1917. The patient at that time had an enlarged mass of glands on the left side of the neck. These were removed by operation, and the enlargement was shown by microscopical examination to be caused by Hodgkin's disease. There was a palpable gland in the right axilla and the spleen was enlarged about 6 cm. below the costal margin. A roentgen-ray examination of the chest was negative for any definite involvement of the mediastinal glands. The patient was treated at varying intervals by crossfire radiation of roentgen-rays. On February 6, 1923, the patient returned to the hospital in a very weak and anemic condition. The glands in the axillæ, neck, inguinal and pelvic regions were considerably enlarged. A roentgen-ray examination of the chest did not reveal any definite enlargement of the mediastinal glands. The patient had a band of scars extending around the chest which were

typical scars of herpes except where some had undergone keloid formation. The patient stated she had had "shingles" two months



FIG. 1.—Case II. Anterior view, showing the eruption extending as far as the midline of the body.



FIG. 2.—Case III. Lateral view, showing the eruption in the axillary regions with quite definite keloid formations.

before admission to the hospital on February 6, 1923. The patient was given another series of treatment, is living and in fair condition today. (See Figs. 1 and 2.)

Summary. Hodgkin's disease; occurrence of intercostal herpes zoster (right side of thorax); late in the infection and without any demonstrable mediastinal enlargement.



FIG. 3.—Case II. Posterior view, showing the scars extending as far as the midline of the body with even more definite keloid formation.



FIG. 4.—Case III. Anterior view, showing the small scars extending as far as the midline.

CASE III.—A.P., male, aged nine years, was admitted to the University Hospital January 7, 1921. Two years ago the glands in the right

side of the neck began to enlarge. For sometime the glands remained the same size but later they began to fluctuate in size and the patient developed fever. At the present time the patient has a glandular enlargement on the right side of the neck, anteriorly, and to a less extent on the left side. The posterior cervical chain is distinctly palpable. Numerous glands are palpated in both axillæ. The spleen is palpable slightly below the costal margin. The inguinal nodes are enlarged. The blood count was as follows: Red blood cells, 3,200,000; white blood cells, 4,700; Hemoglobin, 40 per cent. The von Pirquet test for human and bovine tubercle bacilli was negative. A roentgen-ray examination of the chest showed a mediastinal tumor. A microscopical examination of the gland removed from the neck showed characteristics of Hodgkin's disease (Dorothy Reed type). The patient received treatment by crossfiring applications of roentgen-rays over the involved areas.

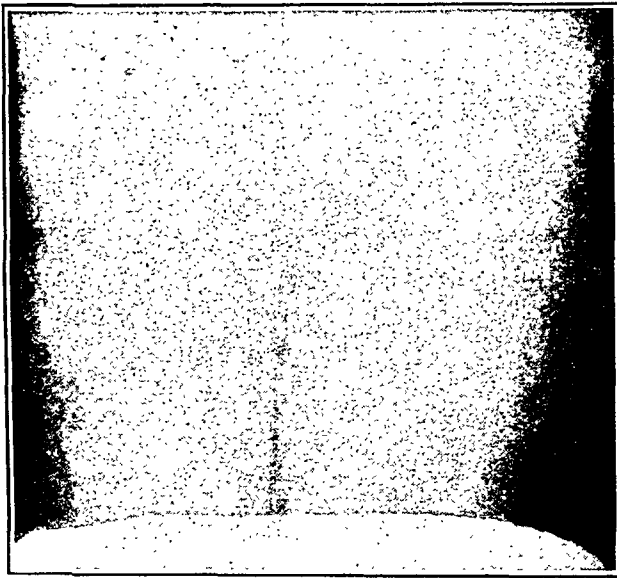


FIG. 5.—Case III. Posterior view of same patient as in Fig. 4.

On April 23, 1921, the patient developed a herpes zoster eruption involving the 9th, 10th and 11th intercostal nerves on the left side. A roentgen-ray examination of the chest at that time showed prominent hilum shadows. The patient is still under observation and doing well. (See Figs. 3 and 4.)

CASE IV.—R. S., female, aged forty-nine years, was admitted to the University Hospital, July 16, 1917. The patient first noticed enlargements on each side of the neck, the axilla and the groin in October, 1916. A roentgen-ray examination of the chest at that time showed mediastinal enlargement. Later the patient developed nodular enlargements over the scalp and an exophthalmos of the left

eye which was thought to be due to an intraorbital growth. After roentgen-ray treatment over these areas, the nodules and the exophthalmos disappeared. These areas have been treated from time to time and the patient continues to remain in good health. In December, 1920, the patient developed a right femoro-cutaneous herpes. Examination at that time failed to reveal any glandular enlargement in the inguinal or the pelvic regions.

Summary. Hodgkin's disease with occurrence of herpes zoster along distribution of right femoro-cutaneous nerve. It occurred late in the affection and at the time no demonstrable enlargements could be palpated.

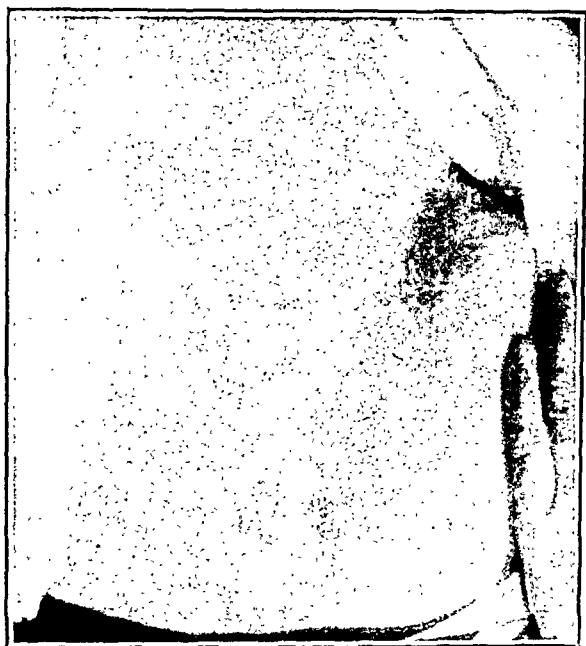


FIG. 6.—Case V. Anterior view, showing eruption under breast, left side.

CASE V.—C. S., female, aged twenty-seven years, was admitted to the University Hospital August 16, 1921. The patient noticed a lump on the left side three months before admission. Very soon after its appearance the lump began to cause considerable pain. The patient was operated on and a bilateralsalpingo-oöphorectomy and supravaginal hysterectomy performed. It was found at operation that there was a general peritoneal metastasis. The pathological report was sarcoma. Later, the patient developed a mediastinal metastasis and also metastasis to the region of Ewald's gland. Under roentgen-ray treatment the patient improved and is living and well at the present writing.

On May 15, 1923, the patient developed a severe herpes zoster which involved the distribution of the 11th and 12th intercostal and 1st lumbar nerves on the left side. (See Figs. 5 and 6.)

Summary. Ovarian sarcoma with extensive metastasis. Patient developed herpes zoster involving the 11th and 12th intercostal and the 1st lumbar nerves, left side. A roentgen-ray examination of the chest and spine was negative for any evidence of growth.



FIG. 7.—Case V. Posterior view, showing eruption on back.

Comments. In Case I, the zoster was typical and occurred on the right side. A large mass could be palpated in the kidney region, posteriorly, on the right side. The active eruption lasted about eight weeks.

In Case II, the zoster occurred on the right side of the chest. Another interesting feature of this case was the keloid formation resulting from the zoster lesions. At the time of the eruption there was no definite mediastinal mass demonstrable by the roentgen-ray. This case of zoster was rather severe.

In Case III, the patient had a light attack of zoster on the left side of the chest. At the time of the attack the hilum shadows were enlarged.

In Case IV, the patient had a slight form of herpetic eruptions which disappeared in five weeks. No enlargement could be palpated at the time of the eruption.

In Case V, the patient had a severe and painful eruption which lasted for eight weeks. The patient has been unusual in that she has responded so well to roentgen-ray treatment in spite of the extensive involvement.

Summary. There are reported 4 cases of Hodgkin's disease and 1 case of ovarian sarcoma in which there occurred an attack of herpes zoster during the course of the disease.

In none of these cases were autopsies performed. The first case died of Hodgkin's disease, the zoster occurring rather late in the affection. In the last 4 cases, which are still under observation, the zoster occurred rather early during the course of the disease in 3 and late in the other. Judging from these cases alone, it would seem that the severity of the disease had nothing to do with the eruption, but that the herpes was probably due to irritation caused by mass of glandular enlargement in close proximity to the ganglion. The occurrence of herpes zoster in Hodgkin's disease, as well as in other malignant growths, is frequent enough to justify its inclusion among the skin manifestations in Hodgkin's disease.

BIBLIOGRAPHY.

1. Ormsby, O. S.: Diseases of the Skin, Philadelphia, Lea & Febiger, 1921, (illustration) p. 356.
2. Van Harlingen, A.: Recent Views of the Origin and Nature of Herpes Zoster, AM. JOUR. MED. SCI., 1902, 123, 141.
3. Casière, M.: Zona feméro-cutane dans un cas de cancer de l'uterus, Ann. de Dermat. et de Syphil., 1895, 5 serie, 6, 892.
4. Head, Henry and Campbell, A. W.: The Pathology of Herpes Zoster and its Bearing on Sensory Localization, Brain, 1900, 36, 379.
5. Blackford, J. M.: Hodgkin's Disease and Sarcoma of the Cervical Glands, Surg., Gynec. and Obst., 1912, 14, 34.
6. Phillips, J. M. B.: Report of a Case of Hodgkin's Disease with Recurrent Fever: A Study of the Literature of this Condition, Cleveland Med. Jour., 1910, 9, 604.
7. Hodgkin: On Some Morbid Appearances of the Absorbent Glands and Spleen: Selected Essays and Monographs, New Sydenham Society, 1901, 173, 161.
8. Longcope, W. T.: On the Pathological Histology of Hodgkin's Disease with a Report of a Series of Cases, Bull. Ayer Clin. Lab., 1903, 1, 4.
9. Longcope, W. T.: Notes on Experimental Inoculations of Monkeys with Glands from Cases of Hodgkin's Disease, Univ. of Penna. Med. Bull., 1907, 20, 229.
10. Symmers, D.: Certain Unusual Lesions of the Lymphatic Apparatus, Arch. Int. Med., 1909, 4, 218.
11. Ewing, J.: Neoplastic Diseases, 1919, Hodgkin's Disease, p. 356.
12. Schamberg, J. F.: Diseases of the Skin and the Eruptive Fevers, 3d ed., 1915, Herpes Zoster, pp. 103-108, W. B. Saunders.
13. Cunningham, W. F.: A Preliminary Report on a Series of Cases of Hodgkin's Disease, Med. and Surg. Rep. Roosevelt Hosp., New York, 1915, p. 235.
14. Osler, W.: Cases of Hodgkin's Disease, Canadian Med. and Surg. Jour., February, 1881.
15. Musser, J. H.: Notes on the Fever of Hodgkin's Disease, Trans. Assn. Am. Phys., 1901, 16, 638.
16. Hall, J. N.: New Growths within the Chest, Am. Jour. Roentgenol., 1923, 10, 185.

THE EFFECT OF MALARIA ON THE NERVOUS SYSTEM WITH SPECIAL REFERENCE TO THE MALARIAL PSYCHOSES.

BY CLEMENT B. MASSON, B.S., M.D.,

ST. ELIZABETH'S HOSPITAL, WASHINGTON, D. C.

HISTORICALLY, Sydenham and Hoffman were the first to point out the psychic troubles of "intermittent fever." Cases of malaria

with mental symptoms observed since the earliest history of the disease are to be found in the literature reported as "an unusual manifestation, a rare case of malaria," and so forth, and unfortunately many of the observations given, though none the less honest, were by men not trained in psychiatry. While the malignant tertian organism (*Plasmodium falciparum* of Blanchard) is generally conceded to be the etiological factor in cerebral manifestations of the disease, from this treatise one finds that, other than infection, there are many factors associated with this, the most dreaded malarial hematozoön, which are productive of mental symptoms.

The type of mental reaction depends upon the acuteness or chronicity of the disease. Somewhat similar to the delirious case of frank lobar pneumonia incarcerated for alcoholic intoxication, the delirium¹ of undiagnosed malaria may be taken for the acute onset of a psychosis and commitment to an asylum, if not carried out, may at least be contemplated. The onset has been found to be very abrupt, occurring even while a person was walking along the street. This may be understood² since infection causes mental disturbances before the rise in temperature occurs, and often delirium subsides after fever has set in. Although this is not the rule, this type of reaction has been observed in malaria. Skliar³ has recently remarked that there are two infectious diseases in which delirium is observed without rise of temperature, namely, malaria and certain stages of variola. Hyperpyrexia following the infection may either cause delirium *per se*, or enhance the picture already present.

Papastratigakis⁴ states that in acute malaria, periods of anguish are intimately connected with the attacks of fever. The patients, without being confused, are a prey to the most distressing anguish, which is not always proportionate to the degree of fever elevation. They have the impression of approaching death and their faces express the condition of a person in great fear. This condition is quite transient, disappearing with the first drops of sweat, and giving place to a characteristic euphoria.

Since it has been observed that the several types of malaria are not infrequently complicated by mental symptoms, no attempt will be made to lay stress upon any particular organism. Sufficient that we recognize plasmodia and the toxins secreted by them, pigment, chemical action of the disintegration of red cells and intoxication due to insufficiency of liver and kidneys in any case of malaria.

To understand the psychoses associated with malaria, I have chosen to attack the problem by treating all the mental observations in the order frequently exhibited by the patient, that is, initial delirium, with or without coma, the psychoses "typical" of malaria with subsequent amnesia; chronic malarial psychosis; pathology of the nervous system in malaria; cerebral malaria with aphasia as

one of its important complications; neurological manifestations and such states as neurasthenia, epilepsy and hysteria.

Initial Delirium. Régis⁵ says that the psychic troubles of the febrile attack consist in an hallucinatory mental confusion of variable acuteness. In the lightest degree there is a sort of subdelirium without total loss of consciousness rather than a true delirium, coming on principally with the period of fever and disappearing shortly afterward in the period of sweating.

At a higher degree the dream-like delirium is realized in the clearest and most typical form. But it is still possible by a brisk agitation, an energetic interpolation, to bring the patients out of their delirium for an instant and to lead them to reality. Ponty⁵ gives his personal experience during the numerous attacks of fever he suffered in Madagascar, and says: "This very clear sensation of awakening at a brisk appeal I have myself felt very plainly and a typical thing, one recalls his delirium, one recounts it like a dream." At this degree the delirium is longer. It persists to the end of the fever and may even prolong itself beyond the period of pyrexia. It is not rare to see it reappear, exactly in the same condition and under the same form, at each new attack.

The delirium may be still more intense, with crying, disordered acts, violence and agitation. It often terminates with death, in convulsions and coma.

Delirium in a pernicious chill attack, although more rare than in the initial periods, was observed by Ponty. The case cited was in a sergeant major who had a typical professional delirium, during which time he lived again his routine army life, such as giving commands, drilling and so forth, ending in death within five hours.

Probably the best contribution to the study of malarial delirium is that of Jean Lecler.⁶ His observations were made at Saloniki in a general medical service where these deliria run their course without the necessity of evacuating the patients to a psychiatric center.

Except for one observation, the clinical picture is constant, at once dreamy and confusional; one finds again disorientation, the hallucinations of action, often professional, the return to reality after an energetic interpolation; then the headaches, the psychic fatigue and the amnesia for the delirium.

Lecler thinks that the mental distress, spontaneous or on palpation of the liver and spleen, is important; for he believes the sense of weight and distress, due to the swelling of these organs, may give rise to misinterpretations on the part of the patient, and hence he explains in part disturbances of sensibility which carry the person affected with malaria toward serious delirium. The state of the liver and its functions merit a longer study, which would explain the similarity of the malarial and alcoholic deliria, as well as the easy alcoholization of malarial cases. Therein lies an etiologi-

factor in mental disturbances associated with malaria, whether they are short-lived delirious states or whether they progress to a psychotic episode.

Folly's⁷ observation upon the role of alcoholism in malarial delirium is valuable. In general, he found that delirium occurred in pernicious forms of the disease; that the initial malarial delirium did not exist in Arabs; that it was only found among alcoholic Europeans. Since the Arabs abstain from alcoholic drinks, save a few natives of cities, and as a class the Arabs are free from the initial malarial delirium, while, on the other hand, the European users of alcohol as a general rule suffer the initial delirium, the reasonable assumption is that alcoholic intoxication is closely associated with and is responsible for the initial malarial delirium to a large extent. Similarly, he found in the Zouaves stationed in malarial districts who were still too young to be deeply alcoholic that, with some exceptions, they too escaped the initial malarial delirium. With Europeans of Algeria, Folly says, the delirium, one might say, is the sign of alcoholism, and in fact inquiry that we have made has always confirmed our preformed opinion. Bearing in mind the frequency of nephritis in malaria, and the possibility of its being complicated by uremia, Folly was careful to eliminate such cases of delirium, and almost all of his cases were of true malarial origin.

As to the types of delirium met with, there were three: It was sometimes pure delirium tremens, sometimes an incoherent delirium with professional hallucinations, sometimes an agitated delirium with epileptiform convulsions.

Régis states that dream-like delirium is not a psychopathic reaction peculiar to alcohol, but represents the characteristic expression of all the intoxications and infections of the organism. Not only from the direct impregnation of the patient's entire body with the malarial toxic injection, but peculiarly due to the insufficiency of the various secretions, particularly of the liver and kidney, do the varied clinical manifestations of intoxication present a similar symptomatological picture.

Coma Following Delirium. The delirious malarial patient may or may not merge into a comatose state, which in turn may end in death or recovery. In considering coma it is to be remembered that while any variety of malarial plasmodium may give rise to this manifestation, the vast majority of cases are due to the estivo-autumnal parasite. Aside from preëxisting conditions in the individual, such as anemia, cachexia, physical or mental fatigue, the puerperium, insolation and alcoholism, the development of coma depends upon three factors: The number of parasites present, the amount of toxin secreted by them and, most of all, the localization in the brain.

Many cases of comatose malaria are reported. Neer⁸ reports 3 cases, 2 having come to autopsy showing the usual findings in the

brain, and a third case of typical estivoautumnal infection without postmortem examination. He states that coma may come on suddenly, like an apoplectic stroke, or may begin gradually during a paroxysm of fever, preceded by slight disturbances in the sensorium, such as apathy, somnolence, restlessness and melancholia. The coma may disappear with the fall of temperature, to reappear again within twelve to twenty-four hours, or it may continue over a period of one to four days, until death or recovery ensues. Tresidder⁹ reports a case of malarial coma lasting forty-six hours, with recovery. The attack was accompanied by epileptiform convulsions and followed by restlessness, delusions of persecution and incoherent speech. The patient recovered mentally within six days. Quaife¹⁰ reports a case of cerebral malaria with recovery after forty-eight hours of unconsciousness. It occurred in a boy, aged eighteen years, employed on a small sailing vessel. He suddenly fell down with violent convulsions and deep unconsciousness. Fresh films of blood showed a few half-grown pigmented malarial tertian parasites. Complete recovery without any complications followed quininization. Graham's¹¹ case was as follows: The patient felt "seedy;" toxic spasms started which became so violent that it was necessary to administer chloroform; there was a period of hyperpyrexia, with blood negative for parasites, and an unconscious period lasting two days. The patient had delusions of persecution for the following two weeks, but eventually recovered. Knowles¹² reports a case of coma in a young Hindu woman which lasted two days, after which, with a period of pyrexia, aphasia developed. Thomson¹³ reports a case which developed suddenly in a laborer while digging in a ditch, whose blood was found to contain many benign tertian parasites.

"Typical" *Psychosis*. Psychoses, *per se*, have been observed repeatedly, both accompanying the attack and as sequelæ. Ascoli¹⁴ says that psychoses from malaria are extremely rare. In the Manicomio, at Rome, they range at the highest 0.5 to 1 per cent. Ascoli, who has probably done more work in malaria than anyone else, sums up his opinion in saying: "Clinical experience demonstrates, then, that malaria causes disturbed (transitory) states of mind, at times also grave ones in its acute onset, that it is able to leave the organism more or less depressed and asthenic, but that of itself it does not give place either to a neurosis or psychosis proper." The frequency of neuroses or psychoses, as Chavigny asserts, is slight, and Kraepelin affirms that they are more frequent in women than in men. The mass of data upon malarial psychoses is large and diverse, due to the facts that the disease infects so great a number of people in both sexes and of all ages, each with his individual personality make-up, and that there are many external factors. To enumerate some of these: Von Krafft-Ebbing¹⁵ saw a case manifesting typical paroxysms of intermittent fever

until after a blow on the head, when an intermittent psychosis with the syndrome of epileptic confusion set in. Manson¹⁶ cites the case of a man who came from Bombay to London, and was placed in an insane asylum on account of symptoms of insanity. Blood examination revealed the diagnosis.

Segard¹⁷ reports several cases of psychic disturbances. In one acute mania with erotic outbreaks lasted three days after a malarial coma of fifty-two hours' duration. In another case a soldier, while recovering from fever, became obsessed with the idea that he was needed at the post, and in an attempt to get there met death by drowning. In a third case a man, who had stood several ordinary paroxysms, one evening during a paroxysm was seized with hallucinations, rushed out and wandered around in the thicket all night.

Pasmanik¹⁸ seems to have had wide experience with malarial psychoses. Among 5412 malarial cases he found mental disturbance 106 times. An hereditary influence was present in none of these cases, and alcoholism in 4.8 per cent. All the cases were depressed. Their duration varied between four days and three months, except in one case of persistent dementia. Pasmanik found soporose conditions to be the most common in children. On exacerbation of chronic malaria melancholia arose and the worst prognosis was in the delirium of cachectics, the result of a relapse.

Gehrenstein¹⁹ found depression most often in malarial psychoses.

"CASE I.—Patient, female, aged thirty-three years; complaining of severe headache, continuously; depression, even to suicide at times; other days she feels better, and performs her usual tasks. When depression gets the best of her she throws everything aside, secludes herself from relatives, sits and prays for hours for her sins. Believes God is punishing her. She begs forgiveness from her neighbors and relatives for insults to them, and repents of her sins. She suffers from insomnia. According to her husband, such periods of severe depression are followed and changed by periods of bettered condition, when she becomes more energetic, works and gives no evidence of depression."

"History showed that in former years she suffered a fever, typical chill, followed by feeling of heat and perspiration.

"Spleen enlarged; palpable to the left under the ribs. Temperature normal; pulse, 72. Laboratory examination for plasmodium on one occasion was negative. However, taking into account the facts of the history, physical and mental, 0.6 gr. quinin hydrochloride, three times a day, was prescribed.

"After having taken 4 gr. the patient returned, stating that in all these days she felt real well; attacks of depression passed, appetite increased and sleep was present. In other words, a noticeable change for the better took place. Following this I did not see her any more, but, according to information, she has improved altogether.

"CASE II.—Patient, aged seventeen years. Mother states the patient has been ill for over a week, constantly going away from relatives and friends, keeping silent to such an extent that even the most insistent questions elicited a reply with very great difficulty. Very passive toward everything, even to her most natural wants. She was liable to sit a whole day without food or drink unless offered her. Answered questions with very marked unwillingness and expressed dissatisfaction, making, when anyone wished to enter conversation, an effort to go away. If persistently questioned she complained of depression and pain. Sometimes she would pace the floor and murmur something for hours in succession. Expression melancholic. Internal organs show no deviation from normal. Menstrual periods normal. No psychopathic heredity noted. According to the mother, the girl suffered all the spring of this year with fever of tertian type. Laboratory examination on the first occasion revealed plasmodia of malaria. Given 0.5 gr. of quinin hydrochloride, three times a day, for four days, with the request for a report at the end of this time. She came to the dispensary much to my surprise alone—happy, full of life, not at all like the girl I had seen a short while ago. Subsequently the condition has not returned.

"CASE III.—Patient, male, aged fifty-two years. Treated him previously for chronic bronchitis; one week ago he suffered for three days with an intermittent fever. The daily attacks have disappeared after medication with quinin. Soon after the disappearance of attacks the patient fell into a dark depression, crying at times, certain that he was suffering with consumption and must die soon. No efforts on my part and those of relatives to convince him that his opinion was all wrong and baseless were effective, and he was insisting upon his early end. He would closely inspect his sputum and would find suspicious symptoms which only he could note. Suffered insomnia, refused food, passed all the time in introspection following his every sensation. Prescribed bromide and chloral and warm baths, but these had little effect on his disposition.

"Temperature during my visits was normal; spleen enlarged but not palpable from under the ribs. With the exception of the already mentioned chronic bronchitis, internal organs revealed no pathological changes. Laboratory examination for plasmodia on two separate occasions gave positive results. Assured then that this was a picture of marked malaria in the form of a psychosis, I prescribed 2 gr. quinin per day for three days, and it could be observed how soon the above described condition was passing. The patient was becoming more energetic and happy. The thoughts that formerly depressed him now looked to him ridiculous. Sleep and appetite better. In a word, this patient after having quinin

went on the road to recovery, although some time after he passed again through two or three typical attacks of intermittent fever.

"CASE IV.—Patient, female, aged twenty-six years, came to the dispensary complaining of precordial depression, which had continued for two weeks. She says that this feeling is so painful and unbearable that she feels herself out of place everywhere; cannot get down to any work, has neglected housework, ceased taking care of her nursing baby and is obsessed by the idea that all this is probably a punishment sent from Heaven for her sins, crying and becoming more and more introspective; according to her husband, the patient showed a very marked change and has turned from heretofore an energetic and good worker to an indolent woman who for hours in succession spoke only of her sin and cried all the time. The expression of the patient is that of misery, frequently sighing and crying. Appetite and sleep absent.

"Temperature normal; spleen slightly increased. Information given by her husband is to the effect that previously the patient suffered attacks of intermittent fever that would pass after taking quinin. Laboratory examination of the blood was negative. Three days' medication with 2 gr. quinin hydrochloride per day brought about a marvelous effect. All the depressive symptoms that tortured the patient have passed. Appetite and sleep appeared; an interest was created in her daily tasks and she returned to work.

"Conclusions: Analyzing these instances, let us note that the psychosis is of a depressive nature. In the first and fourth cases the psychosis appeared in the form of depression with delirium; in the second case melancholic, with stupefaction (*Melancholia atonita*); and finally in the third case it reminded one of hypochondriacal melancholia.

"The preponderance of melancholia in malarial psychoses is difficult to explain except perhaps as observed by me, as well as others, that most of my observations were among women and not in men, and it has been established by others that melancholia is three times as frequent in women as in men.

"Malarial psychoses, by reason of their rarity, might easily escape the attention of a physician and be taken for psychoses, having altogether different etiology."

Chavigny²⁰ states that infection gives rise to varied nervous and mental complications, and the only thing that proves them to be of malarial origin is that quinin cures. There is a disputed question of the relative etiological importance of three factors very difficult to dissociate, namely, predisposition, alcoholism and malaria. He believes these three to be the constant antecedents and further states that it may in part be observed that there is an

exact superposition of the development curve of these psychoses on that of alcoholic intoxication. Finally, he gives as the theory of causation of malarial psychoses that malarial delirium is a toxic delirium, that alcoholism favors the production of the seizures, and that the heredity has prepared a favorable soil for the intoxication.

Régis has observed psychic attacks in subjects of perfect sobriety and Rey affirms the possible absence of every predisposition.

Malarial psychoses, properly so-called, usually take the form, as Régis has shown, of mental confusion or a dream delirium. Clinically, they cannot be distinguished from psychic seizures of alcoholic origin, that is, nocturnal hallucinatory delirium with visions of occupations of terrifying nature. However, hysteria may be set in activity by malaria. Epilepsy, often observed, should be distinguished from uremic convulsions. Neurasthenia is frequent and may take the form of masked seizures or of sequelæ. These three states will be discussed later.

Parot and Gutmann²¹ have done rather extensive work with psychoses caused by malarial infection and consider the mental confusional state to be the initial psychopathy in malaria. Their observations²² were made on Orientals and malarial patients from the north of Africa, and they ignored the acute but ephemeral mental symptoms, which sometimes accompany malarial attacks or act as their equivalents, such as transient oniric attacks, flights, crises of amnesic delirium, hysteriform mimic reactions. These they considered not real psychopathies, but epiphenomena. Although most of the mental syndromes found in malaria are those of current psychiatry, these psychoses nevertheless have their own form, a little different physiognomy, explicable by the nature of the malarial infection and the physiological disorders which it brings on. They found that malarial psychoses are always, at the beginning, confusional psychoses; the confusion may change until it appears as a new syndrome; the stupor is transformed into a catatonic dementia; the oniric monoideism (dream-like delirium with one idea apparently uppermost in the patient's mind) becomes a chronic delirious psychosis. At other times the confusional storm appears in an exhausted organism, the psychic equilibrium of which is fragile, in great waves, maniacal or more often melancholic, which change it into a periodic psychosis.

Malarial mental confusion, which is often cured, is sometimes prolonged in a demential form (the chronic mental confusion of Régis); at other times it is transformed; but these secondary psychoses are always organized about sequelæ of the primary confusion, which represents the framework, final, transitory or temporary. The elements composing this syndrome at the beginning have been very carefully analyzed by Régis and Hesnard. The clinical picture includes the following: The confusional element, with its intellectual sluggishness, its bradypsychia predominating over the

oniric element, the dream delirium; with more sleep than dreaming; perception, orientation, consciousness very much disturbed; psychomotor agitation very slight; the delirium intermittent, not very sustained nor expansive, poor and monotonous. This predominance of asthenic and depressive symptoms, already striking, increases as the affection is prolonged. When the disorientation is dissipated and the awakening begins to take place the nervous exhaustion becomes still more apparent; it is at once both physical and psychical. A profound intellectual weakness, the absence of initiative, severe disturbances of memory, persistent, postoniric fixed ideas tinged especially with melancholy and a marked emotivity are frequent sequelæ which lead to error on account of the neuromuscular symptoms which often coexist. Disturbed reactions, maniacal conditions are sometimes observed, but much more rarely, and are the incontestable result of a constitutional predisposition.

They note the frequent coexistence of somatic nervous troubles, and state that the change in a patient's general condition is constant and serious, since the psychoses only make their appearance in deeply infected individuals.

In one of their typical cases reported a young man developed the syndrome of dementia precox within a year of contracting malaria in Macedonia. No other pathological antecedents were known in the personal or family history, except that he had convulsions as a child. In another case a man, aged thirty-seven years, developed acute mania, but under seven months of sanitarium treatment regained his mental poise, although still somewhat excitable.

Very valuable observations were made by Forrester²³ among the British Saloniki force. Malaria was the biggest factor in mental disease among these troops. It appeared that no new train of symptoms was set up by malaria, and that, in comparison with any other acute specific fever, it differed only in intensity and in the more selective action of its toxins on nerve tissue. The brunt of the attack falls upon the higher cortical centers, giving most commonly symptoms of acute confusion of a cerebral type. He describes two main classes, namely: (1) Psychoses associated with the actual malarial attack; (2) those occurring as a result of repeated attacks.

A study of 32 cases of the first class led him to believe that almost any of the recognized types of psychoses could be set up by the malarial parasite, but one symptom stands out prominently among them, namely, mental confusion. Next in frequency was depression. In every case a period of complete amnesia varying from a few hours to three months was noted. Only 4 of the above cases had hereditary factors.

In Forrester's 87 cases showing mental symptoms as the result

of repeated attacks 1 was returned to duty "not insane;" alcohol accounted for the mental disturbance in 7, while 9 suffered from varying degrees of feeble-mindedness. In the remaining 70 cases in which malaria was the determining factor, it was found that any type of psychosis might be set up. The prominent symptom still was mental confusion; almost equally important in this series was that depression which one would expect to come as a result of prolonged stress and toxemia. Heredity played its role. Of the 24 cases of depression insanity in the family could be traced in 9 instances, while in 31 cases of confusion 7 showed a family history of insanity.

In regard to malarial mental confusion, Papastratigakis⁴ has made his observations among young Greek soldiers who were without hereditary blemish and unacquainted with alcohol. He lays stress upon the abuse of quinin, in that it undoubtedly has a harmful influence on the psyche, and wonders that there is not any treatise in psychiatry on quininic psychoses. In fact, he believes the toxic action of quinin on the nervous elements exceeds by far that of alcohol.

As to confusional troubles, for which the author has proposed the name "malarial mental confusion," they may supervene in subjects without any predisposition, in whom malaria makes up the entire pathological past. Papastratigakis believes it to be essentially a toxic psychosis depending upon anemia and hepatorenal insufficiency. The essential character of the malarial mental confusion is that it is accompanied by certain symptoms which are habitually met in the course of confusions which evolve toward dementia precox, catatonia. Malarial confusion is a catatonic confusion susceptible of cure, which cure may arise between the sixth and eighteenth months. Two cases are cited.

This catatonic reaction was found in Jews as a race more frequently, and bears a definite relation to renal intoxication.

Besides catatonic phenomena, malarial confusion produces in the patient rather frequently aggressive tendencies toward his surroundings. It also causes at times a tendency toward ambulatory automatism. In the course of this confusion there may be noted hallucinations of taste and smell, quite similar to those of systematized psychoses and hypochondriac psychoses. They always accompany a bad functional condition of the digestive tract.

Subsequent Amnesia. Next we have to consider amnesia, which in malarial psychoses is commonly found, as in other infectious psychoses, following the period of initial confusion and more or less conditioned by it. Chabelle in a thesis gives numerous facts proving the frequency of dysamnesia in those affected by malaria, and in this way Régis says the malarial toxi-infection resembles very much infection psychoses where amnesia is, as one well knows, particularly marked.

Manson²⁴ has noted a loss of memory in cases of malarial polyneuritis, and M. H. de Brun²⁵ has of late found amnesia one of the most characteristic features of malarial polyneuritic psychoses. Of the cases studied at the Rueil Hospital almost a third of the patients had more or less impairment of memory. With a primary attack the memory of that period may be permanently a complete blank. One of his patients had no remembrance of anything connected with his stay in the hospital and for several months thereafter.

De Brun found that the malarial subject may also present retrograde amnesia, unable to remember certain periods in his previous life, possibly back into childhood. Some of the men had forgotten completely a foreign language which they had spoken fluently before contracting malaria. Others had forgotten historical events and geography or lost their knowledge of music or mathematics. Skilful electricians could not recall the most elementary principles of physics and electricity, and were unable to install the simplest electrical device. Artisans had forgotten the uses and names of tools.

Carlill²⁶ cites a case of Korsakow's psychosis conditioned by a malarial infection. Goodhart²⁷ cites a case of amnesia in a young school teacher who suffered an attack of malaria during which the accompanying mental symptoms, though mild, were typical. An amnesia for two days remained long after the malaria disappeared.

Chronic Malaria. In chronic malaria the associated psychoses have lost their more or less specific nature and the individual attacks are of shorter duration, though the tendency to recurrence is greater than after a single acute attack. They make their appearance as part of a relapse or may even replace the attacks as psychic equivalents.

Régis⁵ states that invariably in chronic malaria the psychosis is preceded by localized headache. The malarial attack comes on with its clear stages of chill, pyrexia and perspiration or simply one of these, the chill stage in particular.

Delirium in these cases is a typical oniric delirium constituted by action, professional or fantastic, painful, terrifying, or approaching somnambulism. Régis has found in many of his cases that the delirium carries the patient back each time to the epoch of his life where he was taken with malaria, and often it is the same scene that comes back. Interesting are his cases of malaria in soldiers fighting their battles again, killing the enemy once more. As one would expect, disappearance of the delirium leaves the patient a little confused, stupid, with a certain degree of headache and an amnesia for the delirium more or less complete, according to the case.

Next in importance in the psychoses of chronic malaria are those which have for their basis physical and psychic asthenia. They

are those which follow one of the malarial neuroses, in particular neurasthenia, which will be considered later. The psychotic outbreaks, if there may be any sudden flaring up on symptoms, do not appear associated with a relapse of malaria, but rather in the form of a lasting psychosis with variable delirium (polymorphous). Régis has noted in chronic malaria what he chooses to term stupid mental confusion and dementia.

PATHOLOGY OF THE NERVOUS SYSTEM IN MALARIA. To understand better the malarial psychoses let us consider briefly the pathological anatomy of the central nervous system in malaria.

Much has been written upon the pathogenesis of pernicious malaria; postmortem examinations in cases of cerebral malaria are rather uncommon; at least in the literature and from the facts deduced by numerous pathologists, divergent views are held as to the exact pathology. Deaderick mentions four factors which bear directly upon perniciousness: (1) An excessive number of parasites; (2) localization of parasites; (3) toxins secreted; (4) individual predisposition and external etiological influences.

As to the number of parasites, Golgi's law, that the number of parasites determines the severity of the attack, has been generally accepted. Marchiafava and Bignami²⁸ call attention to certain grave cases of comatose, convulsive, delirious or mixed pernicious malaria in which few parasites are found. This would indicate that there are other factors at work in the development of pernicious symptoms.

Localization of parasites may take place anywhere in the central nervous system. The plugging of perforating end arteries as found in the base of the brain and in the spinal cord would, of necessity, lead to the most serious symptoms. A more probable theory is that of Mannaberg,²⁹ who attributes the condition to a sort of agglutination or adhesiveness that holds the infected erythrocytes to the vessel walls. Clinically, the forms encountered are dependent upon the locality in the central nervous system in which occurs the greatest invasion of parasites. Any topographical syndrome may be represented.

Perointzky finds in the cerebrum and cerebellum marked hyperemia of the pia vessels, subarachnoid, perivascular and pericellular spaces and obstruction of the capillaries; their endothelium being swollen with masses of changed red blood cells, which slowly pass through the capillaries, owing to their increase in size and decrease in elasticity, temporarily causing complete thrombosis. These circulatory disturbances lead to punctiform hemorrhages in the gray matter and at the boundary of the white brain substance and necrotic processes in the brain cells.

Weingartner³⁰ cites a postmortem examination in a soldier, aged twenty-seven years. There were purpuric bleedings in the internal capsule, extensive calcification of vessels with inflammatory foci

of a granulomatous nature, such as were first described by Dürck (malarial granuloma). In the adventitial spaces there were deposits of lipofuscin. These secondary hemorrhages, giving pressure and irritation to the nerve cells until absorbed, assume a place in the pathology of pernicious malaria almost as important as the parasites, pigment or disintegrated red cells, giving rise to thrombosis and embolism. They continue a process begun perchance after the organisms have been removed by quinization. In fact, Laveran believes the alleged polyneuritis of malaria is often really a myelitic hemorrhage softening.

The existence of toxin, the product of the malarial parasite, is almost universally assumed by students of malaria. One argument is the existence of coma in malaria without parasites or pigment in the brain. Ewing³¹ says that the majority of cases of comatose malaria coming to autopsy do not show a massing of parasites in the brain. He attributes these cases to general toxemia. However other observers differ.

Deaderick, in discussing pernicious malaria, says that we ought to seek in the conditions of the ground whose quality is so different, and not in the quantity of seed, for the reason which will explain to us gravity of the disease.

CEREBRAL MALARIA WITH APHASIA. Cerebral malaria having a heavy and more general segregation of parasites in the brain may assume the form of any brain disease, and is frequently found in malarial districts. The estivoautumnal parasite is most often the etiological factor, yet the benign tertian may be the cause of these grave disturbances. To attempt a classification of the cerebral forms would serve no useful purpose in this paper, but emphasis must be placed upon the fact that mental symptoms very frequently accompanying such forms of the disease are not commensurate with the cerebral trauma, due to parasites *per se*. Jones,³² in discussing one phase of the subject, says violence and irrational behavior are more frequently noticeable in these patients than they are in cases of hemiplegia of the usual hemorrhagic or thrombotic origin. Many interesting cases of cerebral malaria are given in the bibliography.

Of the cerebral manifestations motor aphasia, produced by blocking of the capillaries of Broca's areas by parasites, pigment and other matter for varying periods of time, with occasional secondary effects, such as hemorrhage and softening of the part, is the most interesting and possibly the most rare.

Rao³³ cites a case in a male, aged nineteen years, who suddenly vomited, fell down, became unconscious and was found to have lost his speech upon regaining consciousness. Plasmodium falciparum was found in his blood and after being given quinin by hypodermic injection for three days he regained his speech as suddenly as he had lost it.

The benign tertian parasites may also give rise to this complication as in the case cited by Dec,³⁴ in which aphasia lasted ten days. Following two days of chills and fever the patient lost his power of speech. Tertian parasites were found in his blood, and under quinin therapy he regained his speech.

Browne-Mason³⁵ reports a case of malignant tertian malaria complicated with motor aphasia of longer duration than either of the foregoing cases. After suffering fever for four days the patient "became without speech," and while he could not speak, yet he could understand what was said to him when vigorously aroused. Twenty-five days later the patient had regained his speech.

Gillot³⁶ believes aphasia, isolated or associated with other paralyses, is the most curious, although the most rare of the manifestations of malaria acting on the cerebral centers. Here is a case of motor aphasia he quotes as a complication of tertian fever, of interest because of its short duration: A school teacher, who had just had tertian malaria, suffered cephalic congestion more intense than usual on one occasion. Suddenly it was impossible for her to move her right arm, and she was unable to call out. While she easily recognized her husband, heard and understood his words, it was totally impossible for her to make reply. This hemiplegia with aphemia lasted for three hours. There were no hysterical stigmata present; malaria was the only cause.

Gillot says that it is not impossible to see the aphasia renew itself in intermittent fashion during consecutive attacks. Possibly passing aphasia may be the only manifestation of a larval form of malaria.

NEUROLOGICAL MANIFESTATIONS. Passing notice may be given to the neurological manifestations of malaria not frequently seen, yet of value to acquaint one further with the action of malarial toxin. The complications may be divided into peripheral, medullary and central.

Of the peripheral complications, we have neuralgias and neuritides. Jones³² has published his interesting findings on segmental hyperalgesia in malaria, and in brief he found that of 120 cases examined for this sign 70 per cent were positive. Of the 83 cases, this sign was 100 per cent positive in the seventh dorsal area, but varied infrequently above and below this area. Cases of neuritis of malarial origin are numerous in the literature, either simple or multiple in type.

Paralysis of the vagus center in the medulla is the cause of sudden death in malaria and transitory paralyses, such as motor aphasia, are occasionally met with in the literature. Heat stroke, which may and frequently does progress to coma, is reasonably supposed, as Milner points out, to be due to intoxication of the heat-regulating center. He also points out that once this apparatus is upset the body will assume as nearly as possible the temperature of the

atmosphere. Heat stroke does not supervene because sweating ceases, but the patient ceases to perspire because he has got heat-stroke and is suffering from paralysis of the heat-regulating center. In fact, Milner³⁷ would have us believe that heat stroke, as a clinical entity, is non-existent and that it is nothing more than a symptom of malignant tertian malaria, and in support of this view he gives some admirable observations. Chavigny says that quinin may cause transitory paralysis of medullary origin, and that it is difficult at times to distinguish between the effects of alcohol and syphilis.

Both upper and lower motor neurone paralyses are found in connection with malarial infections. Blin and Kerneis³⁸ report a case which resembled anterior poliomyelitis in many ways, and, in fact, was regarded as this disease, but was really due to malarial infection of the nerve cells of the anterior horns of the cord. Many cases of monoplegia and hemiplegia of central origin are reported in the literature.

A counterpart for the peripheral neuralgias is found in the usual headache accompanying malarial fever. In some individuals the headache is severe, and as such is a forerunner of coma. Stedman³⁹ reports a case of malaria in which severe paroxysms of headache were the only symptom. Ettinger also reports 3 cases of malaria in which severe headaches were the most prominent symptom.

That there is a central component comparable to peripheral neuritis seems to be obvious. Manson remarks in his book that loss of memory, partial or complete, appears to be a common accompaniment of peripheral neuritis of malarial origin. Since Korsakow's psychosis is found in cases of alcoholic intoxication showing polyneuritis, a case of Korsakow's psychosis of malarial origin, as described by Carlill,²⁶ would seem to strengthen the assumption.

Malarial Tremors. Closely associated with neurasthenia, and sometimes a symptom of it, is the malarial tremor, however, the condition has been found by some observers as a separate entity.

De Brun's⁴⁰ observations were on cases without the slightest suspicion of alcoholism, neurasthenia, exophthalmic goiter or any other affection capable of producing a tremor. As a general rule, both upper limbs were affected equally; the tremor was not strictly limited to the upper limbs, but other parts of the body are much less affected. He found that intentional movement, prolonged effort or emotion, considerably aggravated the tremor; that the malarial tremor was essentially unstable and frequently underwent rapid changes in its intensity, not only from one day to another, but even in the same day, often without appreciable cause; and finally he believed it to be due to an infectious toxemia.

Jourdran⁴¹ agrees when he says that he has not found the malarial tremors to be a persistent symptom and believes them properly classed as toxic tremors. He also states that the tremor which he observed in a very clear case could not be compared to the

chill which often marks the initial stage of the attack; that it disappeared completely with the cessation of the attack, and that malaria may, like intoxication, give rise to a tremor that should not be confounded with other known forms observed in diverse diseases or disturbances of metabolism. Boinet has published a case of tetaniform tremor of malaria; Lemoine and Chaumer, a Parkinsonian phenomenon; Boinet and Salabert, a malarial chorea. Fornaca⁴² reports a case of malarial tremor, not affected by active muscular effort, neither increased nor decreased. The tremor was accentuated with the periodic occurrence of fever and was differentiated from a chill even by the patient himself.

NEURASTHENIA. Neurasthenia accompanying malaria, and conditioned by a low-grade infection over a long period of time with occasional exacerbations, is quite frequently observed.⁴³ Pope says that in chronic malarial cachexia the nervous symptoms are most marked and neurasthenoid in character. However, all mental and nervous symptoms are less in degree than in the neurasthenia. There is general depression, irritability and nervousness, and a tendency to emotionalism. Numerous somatic complaints, such as vertigo, insomnia and headache, have for their basis vascular disturbances.

Atkinson⁴⁴ states that the victim of this postmalarial condition is in a pitiable plight. He is a physical and nervous bankrupt. His defenses are all spent; the very fountain of his sustenance—his hemopoietic function—is vitiated at its springs; he suffers from a dozen inroads upon his debilitated system and is an easy prey to a dozen others. He is frightfully depressed and without ambition.

A very illustrative case is reported by Musgrave⁴⁵ in an army officer, aged forty-two years. His initial infection was in Cuba, in 1898, and after that time he had numerous attacks of what later proved to be tertian malaria which finally led up to a neurasthenoid condition. In 1909 the patient thought he was going "insane," complaining of mental and physical debility. He was invalided to the United States from the Philippines with a diagnosis of melancholia and severe cerebral neurasthenia. Authorities at that time recommended his transfer to an insane asylum. He was mentally depressed, tended to be seclusive and complained of photophobia which was marked, especially during an attack, and continued until the real cause was found and treated. At one time the patient was in need of constant attention. Before the cause of his behavior was known the patient was about to be courtmartialed for malingering.

EPILEPSY. Malaria has varying effects upon those predisposed to epilepsy and upon those suffering from the disease. Cases have been called to my attention in this hospital in which the patient attributed to malaria the beginning of his epileptic attacks. These might be disregarded, but facts point to the possibility of there being an element of truth in their statements.

Francis Hare⁴⁶ believes there is a well-marked malarial epilepsy, and refers to cases mentioned by Jacobi, Payne, Hamilton and others to the effect that such occur occasionally in the Southern States and in Brazil. "In Hamilton's case a young man, who had lived for many years in an exceedingly malarious region, had more or less periodic epileptic attacks, attended with great preliminary rise of temperature and intense congestion of the face and head. . . Change of the place of habitation and the use of quinin removed the disease entirely."³ We imagine that the intense cutaneous vasoconstriction, associated with ague paroxysms, may in some circumstances develop so rapidly and widely as to preclude adequate compensation by the muscular vasodilatation of rigor and so lead to vagus inhibition of the heart. This view is, I think, fully recognized by Broadbent, who points out that the cold stage of malarial fever may be carried to such a degree as to bring the heart to a standstill and produce fatal syncope or serious nervous complications.

Epileptic attacks are held to differ from rigors mainly in the nature of the compensation for the extensive vasoconstriction common to both. Trousseau regarded rigor as convulsion minus the cerebral phenomena. The view adopted explains the absence of cerebral phenomena from rigor; muscular vasodilatation anticipates cardiac inhibition: Thus the occurrence of rigor prevents (in a strict sense) the occurrence of convulsions.

So that in those of a neuropathic disposition the vasoconstriction occasioned by a malarial paroxysm may be of such extent as to cause vagus inhibition of the heart which may result in epileptiform convulsions.

Régis⁵ states that malaria ameliorates epilepsy at times. This action is rare, although more frequent than in hysteria. It awakens, aggravates and provokes epilepsy. Malarial epilepsy does not present any distinctive character.

Marandon de Montyel,⁴⁷ who has done considerable work on the subject, believes, from a series of 14 observations in the course of eleven years, that malarial fever does not lessen attacks in epilepsy. In 5 cases of mild epilepsy, with slight attacks at long intervals and with little mental impairment, the symptoms were aggravated during an intermittent fever which yielded readily to quinin. In 3 cases in which there had been no convulsive seizures for a number of years the attacks returned under the influence of malarial infection. In the remaining 6 epileptic attacks occurred for the first time while the patient was suffering from malarial infection, and in another they were worse under the same condition, although they occurred also independently. In a third epileptic whose attacks developed during a second relapse of malarial fever the attacks recurred, and the patient remained delirious after the malarial fever was cured. The patients in the remaining 3 were

addicted to the use of alcohol, but this was considered merely a predisposing factor in 1 case and the exciting factor in the other 2, the malarial infection operating, however, as an aggravating influence. It should be added that all of the patients possessed a neuropathic disposition.

Hysteria. Hysteria in relation to malaria holds a place quite similar to epilepsy.

Regnault⁴⁸ quotes a typical case of hysteria provoked by malaria, and in conclusion states that if the intermittent fever can produce trembling and paralyses, as several cases reported by Bonnet in the *Revue de Médecine* testify, it is only the provoking cause. The effective cause then is hysteria, and one will search for the diverse symptoms of it whenever one sees a case of paralysis or of trembling, even appearing under the direct dependence of an acute infectious malady.

Roux⁴⁹ states that it is an actual fact well known that malaria must be counted among the number of provocative agents of hysteria. He is unwilling to say that malaria could be the sole cause of hysteria or whether it merely fosters the development of such a neurosis. His observation on a case that he reports favors the last point of view, and is interesting especially because of the mode of evolution of the neurosis. Manifesting itself at the beginning in a non-convulsive form, which gave to the malarial fever a particular character of perniciousness, it terminated during convalescence with typical crises of convulsive hysteria. These pernicious attacks represented thus an exaggerated mode of reaction of a predisposed organism under the influence of malaria. This reaction was shown by nervous symptoms, which in one patient disclosed hysterical phenomena, and this hysteria, until then latent, manifested itself during the attack of malarial fever. The nervous crises find an explanation in the malarial anemia which "provokes the manifestation of the neurosis in predisposed subjects besides by their personal or hereditary antecedents" (Laveran).

Régis quotes the conclusions of his pupil, Commeleran, on hysteria: "Malaria appears to be susceptible of ameliorating hysteria, but this action is altogether exceptional. It awakens and aggravates a preëxisting hysteria. It provokes the manifestation of the neurosis—most often in predisposed neuropaths and in some cases in subjects who have no morbid antecedent, personal or hereditary. In the first case the neurosis thus provoked offers few special characters. It is especially convulsive, with incomplete crises and hyperesthesia. In the second it seems to particularize itself: (1) By the presence of an hysterogenous zone at the level of the liver or of the spleen, according to the organ which is most often affected by the infection; (2) by the predominance of the hysterical phenomena in the half of the body corresponding to the

hysterogenous organ. It seems that it would be necessary to take account of hysteria in certain pernicious attacks and some of the postmalarial paralyses."

Marandon de Montyel⁵⁰ reports 8 cases of hysteria associated with malaria observed over a period of twelve years, and states that there is not malarial hysteria any more than there is malarial epilepsy. For the two malaria is a provoking agent. In 1 case that he reports there was a notable aggravation of benign hysteria twice a year with the return of malaria. In 2 cases hysteria was reawakened by malaria after a quiescent period, 1 so long as eleven years. Discounting the family and personal history as given by the patient, and laying more stress upon his physical and psychic stigmata, we are enabled to see that malaria acts powerfully to provoke hysteria.

As to the time factor, hysteria is aggravated immediately by malaria; to recall a preëxisting neurosis that has disappeared for several years the organism must suffer a greater amount of malarial poisoning; to provoke this neurosis it was often observed to take five, twelve and eighteen years.

Case Reports. In 5 definitely psychotic patients at St. Elizabeth's Hospital I have observed attacks of frank malaria, and in the records have found 7 similar cases. Four of the 12 cases were diagnosed tertian malaria from blood smears, while the remaining number were not typed. Prompt quininization in a few of the cases must be considered as a preventive in the development of psychotic symptoms. The mental examination of these patients was incomplete and amounted to a casual observation of their status, sufficient, however, to assure one that the malarial infection neither ameliorated nor aggravated their mental symptoms, nor added to those already present. However, from the foregoing, the hereditary or acquired nervous and mental imbalance factor in malarial psychoses appears to assume none the less an important role, explained on the following basis. These patients had made a hospital adjustment and were not so easily disturbed by a toxic agent which to one fighting life's battles with an inferior nervous system and personality make-up might have proved the last added force needed to take them out of reality.

The following 3 cases of psychoses associated with malaria have come under my personal observation and have been studied thoroughly:

CASE I.—A. B. P., a private in the Marine Corps, a native of Spain, aged nineteen years, well developed, weighing 169 pounds, exhibited no defects on physical examination save a slight mitral leak that was well compensated.

History. Neither organic nor psychiatric determinants were present in the family history. The patient was born in Camillas, Spain, in 1904, the youngest of five. His birth was normal, and he had been breast-fed. He had had no diseases of childhood; he began school at the age of five years and completed the eighth grade at the age of thirteen years. There was nothing of note in his early youth until the age of thirteen years, when, because of punishment in school, he left home. It seems as though his strongest urge was nomadism, for from this time on he worked as kitchen boy on transatlantic liners. He held many jobs, always doing his work well, but he was inclined to give up and "rest awhile," as he expressed it. During these rest periods, which occurred every six or seven months, most of his earnings were spent in gratifying his sexual desires. He had his first heterosexual experience when fourteen years of age, and continued at regular intervals, but denied homosexual practices.

He joined the Marine Corps in 1920 to become an American citizen. He drank excessively at times, but never had delirium tremens. From his service record the following was abstracted: At Slatto-Mayor, late in the summer of 1921, the patient had a light attack of influenza and tropical lymphadenitis; at San Pedro de Macoris he had dysentery (unclassified). In December of the same year malaria was diagnosed from the blood (type not given). The patient had a chill with a temperature of 104°, and was treated with quinin (15 gr. three times a day); he was returned to duty, December 31, 1921, with orders for continued quinin treatment.

From the patient's own story he must have lost his mind at that time, for he remembered nothing from January, 1922, until June 14, 1922, when he was admitted to St. Elizabeth's Hospital and was told the date and where he was. His service record, dated April 21, 1922, gave the diagnosis psychosis, unclassified. The patient was in confinement for several months, and talked irrationally. He was disoriented in all fields, did not know his name, was very restless, but apparently in good physical condition.

His record states as follows:

April 22, 1922: Insomnia; refuses food; destructive to clothing; yells and sings continuously.

April 23: Becoming more violent; restrained.

April 24: Attacked the guard.

May 1: No improvement.

May 8: Not quite so active; Wassermann negative.

May 7: No improvement; some days he is quiet and sullen; others, very noisy and hilarious; not destructive to clothing.

May 20: Subject to moody spells; no evidence of violence for some time.

May 27: Transferred to the States; caused no trouble except when he saw a negro. This seemed to enrage him and he would attempt to strike the negro. Sleeps and eats well. Vocabulary increasing. Seclusive.

At the United States Naval Hospital, Norfolk, Va., the patient's psychosis was unclassified. The patient was mute, restless, destructive, smiled at examiner and answered "chow;" made his desires known by signs; was greatly excited at the sight of a negro, but quiet at other times; apparently reacting to hallucinations and delusions.

June 7: Quiet, mute, completely disoriented.

June 14: Upon admission to the United States Naval Hospital, Washington, D. C., the patient was inaccessible, out of touch with his environment and repeated "chow poo" frequently; emotionally unstable, introverted and seclusive. Stated he hated negroes and would kill them.

Late the same day he was transferred to St. Elizabeth's Hospital, where he complied with routine procedures. When interviewed he was found totally disoriented; he thought he was in Santo Domingo and that it was January, 1922. When told the name of the city he was in, the month, and so forth, he evinced great surprise and wanted to know where he had been for the past six months. He remembered being placed on the sick list, December 23, 1921, suffering from malaria. His head was "big" and he had fever; he was returned to duty, and about January 5, 1922, vaguely remembers being sent to a hospital, but that is all. When questioned about negroes he gave out some paranoid ideas regarding them and explained that the reason why he had more trouble with them than the other marines was because he, speaking Spanish, could understand their speech and resented their referring to the marines in derogatory terms.

June 21: Blood Wassermann test and routine urinalysis was negative.

June 29: Blood analysis: Hemoglobin, 80 per cent; erythrocytes, 4,720,000; leukocytes, 7240; polymorphonuclears, 33 per cent; lymphocytes, 64 per cent; eosinophiles, 3 per cent. No malaria organisms were present.

During his stay on the admission service he accused a nurse of having his sombrero (which he never had), and on July 1 he was observed to be somewhat disturbed and apprehensive; he had little to say and expressed the idea that he was to be returned to San Domingo. It was brought out that this occurred to him when he saw two marines who came to the hospital for some personal effects of a former patient.

On August 2, 1922, mental examination brought out nothing psychotic save a period of amnesia lasting from January, 1922, until June, 1922. The patient was granted ground parole, August

18; he abused none of his privileges, and, due to his dependability and thrift, was granted city parole, September 22.

The patient has been adjusting well; he is bright and cheerful, and keeps occupied during the day; he wishes his discharge, so that he may get a job on a transatlantic liner before winter sets in.

This is a case of psychosis in a male adult in which malaria seems to have been the chief factor. No hereditary determinants present themselves. Nomadism and a tendency to excessive drinking are factors which might well indicate a somewhat unstable make-up. The former fault exhibited itself in boyhood, and the latter seems to be not deeply rooted. The patient explained that the natives were afraid of the marines, so that frequently they would go to a native store, getting all the liquor they desired on demand. As he reviewed these happenings, he gave the impression that he had indulged in a youthful prank, and was not a seasoned drinker.

Now that this patient has cleared up entirely, he gives the impression of being of quite a stable make-up. As regards stressful circumstances, these seem to be lacking, for he was well liked by his equals and superiors. He made friends with those of his own rank, and enjoyed being in their company. In fact, he was of special value to his commanding officer, because of his knowledge of Spanish. Alcoholism was certainly a factor, together with his malarial infection, and the combined effect has been observed to bring on just such a mental upset as this patient exhibited. His confusion, hallucinosis and amnesia are typical, save that his amnesia was over a period much longer than any cases found in the literature.

CASE II.—E. M., an adult white male, aged thirty-four years, weighing 156 pounds, developed mental symptoms following an attack of malaria in November, 1921. Physical examination revealed nothing abnormal, and he was in a fair state of nutrition. The blood Wassermann test was negative, and urinalysis showed a few hyaline casts, but was negative for sugar or albumin.

No psychopathic determinants were elicited in his family history, and his family life was free from mental conflicts. As a child he was puny, pale and anemic, and because of his poor health he was kept from school until late in his second decade. His attendance at school was intermittent, and he never went continuously for more than five months; he left school when twenty-one years of age, having completed the third grade. He seems to have made a good economic adjustment, working on a farm until drafted into the army in 1918, where he served until after the armistice. Not being satisfied with farm life after his sojourn overseas, he enlisted in the Marines in April, 1921. He was sent to Haiti, contracted malaria on November 20, 1921, and before full convalescence he began to show mental symptoms, the most prominent of which was

marked depression. The patient stated that he had always been a heavy drinker since childhood, and that he could drink a large quantity of whisky a day.

On March 17, 1922, the diagnosis was made of dementia precox, and March 31 he was transferred to the United States Naval Hospital at Norfolk, Va. Admitted on April 13, he was fully oriented, easily confused, disinterested in things about him, and would remain in one position for hours at a time. No hallucinations or delusions were elicited at that time.

On April 24 he was transferred to the United States Naval Hospital, Washington, D. C., where he was noticed to be greatly retarded, introverted and almost inaccessible, mildly catatonic, depressed and apparently was reacting to delusions. At the hospital he suffered a relapse of malaria (due to *Plasmodium vivax*). He acted peculiarly; entertained persecutory ideas and tried to escape; became disoriented and apathetic; was deteriorated and exhibited mild *cera flexibilitas* (waxy flexibility). He was markedly retarded, disinterested, and only talked when questioned; he denied hallucinations at that time.

On April 26 he was admitted to St. Elizabeth's Hospital in the same condition. He said he thought there was something wrong with his head, and had a dizzy feeling at night. Things appeared before his eyes at night—animals, "varmints," faces of his kinsfolk; he had auditory hallucinations of his mother's and other people's voices. At times the voices called him bad names; he seldom was hallucinated in the daytime, and was not positive of persecutory ideas.

Upon entering the examination room, May 18, the patient presented an unkempt, untidy appearance. He walked in a listless, languid manner; was coöperative, but quiet and introspective; he showed psychomotor retardation, and approached the condition of catatonia. He was confused during the examination; had slight insight and his judgment was defective. Memory for recent and remote events was poor and numerous other mental tests showed him to be defective. Visual and auditory hallucinations of his kinsfolk were present; paranoid ideas were lacking, and he was disoriented in all fields.

On June 1 the patient appeared fairly well nourished; he was in a state of agitated depression; picked at his clothing continuously and admitted auditory hallucinations. He spoke in monotones in a meagre somewhat irrelevant manner; he was untidy in his appearance.

On July 14 the patient had a frank chill, following which his temperature rose to 106°. Quinin treatment was instituted immediately, consisting of 45 gr. a day for one week, and 15 gr. a day for a week thereafter. At 8 o'clock the following morning the patient's temperature was normal and has remained so since that

time. The urinalysis was negative. The blood count showed: Erythrocytes, 3,130,000; leukocytes, 6000; polymorphonuclears, 79 per cent; lymphocytes, 21 per cent; large numbers of *Plasmodium vivax*.

Hyperpyrexia and quinin therapy did not aggravate his mental symptoms.

When examined, July 26, the patient stated he felt very much better. He was correctly oriented; his speech was retarded and monosyllabic. He was somewhat apathetic, and referred to having heard voices in the past, but denied them at present; he had slight insight. On August 26 his blood was entirely normal; no parasites were found.

On September 22 it was noted that the patient had made slow improvement, which began soon after quinin therapy was instituted. While he was still retarded he took more interest in his surroundings, paid better attention to his personal appearance, was correctly oriented, and stated that he felt very much better. No definite delusions and hallucinations were elicited.

Physically he appeared somewhat undernourished.

Undoubtedly this patient had a strong predetermining factor, as shown in his early backwardness physically and mentally, his addiction to alcohol and his failure to readjust to his former occupation and his desire to wander about. Nevertheless, it seems from the history of the case that one must attribute to his malarial toxic infection the additional factor in the development of his psychosis. He did not react to this toxic condition by delirium and acute hallucinosis, as is noted in some cases; but very likely his psychosis took the path of least resistance and showed itself in catatonia. That he improved slightly after his first treatment with quinin is evident. However, a relapse of malaria brought on an aggravation of his mental symptoms, and with quinization for the second time he again showed mental improvement. Whether he ever entirely recovers is doubtful, and he may be well classified a case of dementia precox; however, it is obvious that malaria had more than a casual relation to his psychotic manifestations.

CASE III.—A. B., a retired army sergeant, aged fifty-three years, but in appearance much older, in a poor state of nourishment, quite cachectic, was admitted to St. Elizabeth's Hospital, August 10, 1922. His family history was negative for psychiatric determinants; also his personal history was negative until he entered the army at the age of twenty-one years. He says he enjoyed army life; he was courtmartialed three times for being absent without leave and for "booze fights" during his long army career. He drank moderately all his life, but very occasionally became intoxicated.

While in Cuba, in 1898, he contracted malaria, and was sick for

three weeks, but had no mental symptoms. Since that time he has lived without chills for several years at a time, but in general was able to predict the onset of chills every fall. In 1903, during a relapse, he became erratic for a short time during the febrile period.

In October, 1921, the patient, while at Letterman General Hospital, was diagnosed as a case of psychoneurotic hysteria, from which state he recovered and was discharged, November 8, 1921.

After suffering chills and fever for a week the patient was readmitted to the same hospital. Examination at that time found him very much undernourished; all superficial lymph nodes were enlarged; arteriosclerosis was present; his blood-pressure was 180/140 mm.; his spleen and liver were enlarged. The patient comprehended questions poorly, and had a poverty of thought. Occasionally he was restless and agitated; he had changeable delusions and mild auditory and visual hallucinations. He was confused and disoriented as to person, with marked fabrications of memory. The blood Wassermann test and neurological examinations were negative.

The patient was quite confused when admitted to St. Elizabeth's Hospital, and did not know why he was sent to such an institution unless because of confusional states. On August 15 he was found fairly well oriented with slight clouding of memory; retarded in speech and action; emotionally somewhat depressed. His insight and judgment were very good, and aside from occasional confusional periods he seemed quite normal mentally. Physically, he was very anemic; had a cachectic appearance; his spleen was enlarged, and his heart enlarged to the right with a presystolic murmur, heard at the apex. Urinalysis and blood Wassermann test were negative, as was his blood for malarial parasites.

When interviewed, August 24, he was found to be readily made nervous; in fact, ordinary conversation or taking his blood-pressure was sufficient. While in bed he exhibited a very marked tremor in his voice, also in both arms and hands, and even in his neck muscles. He gave the impression of being run down, both mentally and physically. The blood count bears this out: Erythrocytes, 2,170,000; leukocytes, 5600; polymorphonuclears, 21 per cent; lymphocytes, 78 per cent; transitionals, 1 per cent; no malarial parasites present. Urinalysis was negative. Roentgen-ray on August 26 showed the spleen to be moderately enlarged. There had been a low-grade fever (100.4° F.), with remissions. A second blood count on September 6, after the patient had received general supporting treatment, Bland's pills and quinin, showed: Erythrocytes, 2,880,000; leukocytes, 4600; polymorphonuclears, 25 per cent; lymphocytes, 70 per cent; monocytes, 3 per cent; eosinophiles, 2 per cent; no malarial parasites.

The patient, when examined, September 27, 1922, said that at

times his mind would go blank following a chill. Although he still suffered physically from his chills, his mind now seemed to bear the brunt of the attack. A fear reaction came over him at the time of a chill, and he wished himself in bed, where he knew he would be safe. Said he felt weaker than ever before, and feared lest he should lose his mind. At this point the patient showed considerable emotional effect; he became lachrymose, and with this his tremor became very pronounced. He said that if he had a chill early in the evening he found himself very confused that night, troubled with mild visual and auditory hallucinations. His consciousness seemed to be clouded, as he was retarded mentally and disoriented spacially. His memory was poor. He knew that for the last eighteen months he had had relapses of malaria more frequently and that he had been more confused. His stream of talk was free, relevant and coherent.

There was a gradual decline of his physical condition, with death on October 8, 1922. Autopsy, seven hours postmortem, revealed double bronchopneumonia with double pulmonary edema, acute cerebral anemia, general anemia, hypertrophic hepatic cirrhosis, chronic parenchymatous nephritis and chronic atrophic gastritis.

This case was a classical chronic malarial cachexia brought on by early infection, with frequent relapses. Alcohol played an important role, accompanied by malarial toxins. That he should have been diagnosed as a case of psychoneurotic hysteria seems to have been not far wrong, but does not give any information as to the possible cause of such a psychosis. His tremor and emotional instability are in keeping with chronic malarial cases, due either to a neurasthenic or hysterical development.

The following cases have been abstracted from the hospital records. The first is a case of cerebral malaria, with an autopsy report.

CASE IV.—C. C., aged thirty-four years, was admitted to St. Elizabeth's Hospital from the army, April 21, 1875, with no record of a routine physical examination being done at that time. No family history was available; mental diagnosis, chronic dementia for one year and six months' duration. On October 7 the patient had a chill and was confined to bed, but got up four days later. No diagnosis mentioned or kind of treatment. In December of the same year note states that the patient was up, assisting with the ward work; was quiet and orderly.

No further notes are found until May 1, 1900. At this time the patient was able to walk about, was quiet, rather seclusive, clean in his habits and assisted with ward work. In August, 1900, the patient was put to bed suffering from a chill. He received "ague

mixture" until August 9, at which time the patient felt very comfortable.

Again on September 11, 1902, the patient's temperature reached 102.4° with pulse and respiration in proportion. A laboratory report was positive for estivoautumnal malaria, September 10, 1902. He received "ague mixture" for four days, at which time his temperature remained normal, and he got up and dressed. In October of the same year the patient's mental notes show no change in his condition.

In March, 1903, a note states that the patient was quiet and orderly and helped with ward work; he was seclusive, and of a moodish disposition; physical condition was very good.

In April, 1904, the patient was quite eccentric, remained mute unless spoken to, and spoke in a whisper, but assisted with ward work. No change was noted in 1905 or 1906. In 1907 his habits were fairly tidy; he assisted with light ward work, and seldom complained. In 1908 he showed no change. On January 24, 1909, the patient was very quiet; he remained mute, unless spoken to, and then answered in a whisper; he was fond of reading, and took some interest in his surroundings; psychomotor retardation.

In 1910 the patient enjoyed walking about the lawn; his health was good. December 20, 1910, urinalysis showed very few hyaline casts. There was no change in 1911 until May 15, when the patient had a chill (temperature, 100.4° ; pulse, 106; respirations, 24), with remissions continued for three days, reaching its height, 103° , on May 17. He received quinin, 5 gr., every six hours. On May 18 the patient showed psychomotor retardation; hallucinations did not seem to be present; the examiner was unable to learn of delusions since the patient would not talk. Urinalysis on May 22, 1911, was negative.

On June 1, 1911, the patient was quite seclusive, introverted, neat and tidy. On October 7 the patient had a recurrence of malaria; he was put to bed, but was able to be up again on October 10.

November 9 the patient was quite sick; he had edematous ankles, with a rise of temperature and anorexia. He seemed to have little use of his muscles; the temperature rose to 104.4° . On November 12 it came down to normal, returning to 103° at the time of death.

Summary of autopsy report: The brain showed the basilar vessels were slightly sclerotic. The whole brain was hard. On section the gray matter of the cortex and central ganglia was congested. No softenings or gross lesions were found. The heart was normal. The lungs showed hypostatic congestion. There was fatty infiltration of the liver and chronic diffuse nephritis. The spleen was enlarged; the pulp was soft and jelly-like and gray-reddish in color (malarial spleen).

Microscopically there was neurophagia of a few ganglia cells. Hyperplasia of neuroglia tissue was very marked. The vessels

were dilated and congested, and filled with malarial parasites. These were confined to the interior of the bloodvessels; the lymphatic spaces were not infiltrated.

Clinical diagnosis: Undifferentiated psychosis (dementia); cerebral arteriosclerosis.

Anatomical diagnosis: Cerebral arteriosclerosis and malaria of the vessels of the brain.

This patient evidently suffered from malaria for some time before admission, and was continually fighting malarial toxins which were at times made manifest by objective symptoms. His mental examination was meager; however, he was an institutional case suffering from a malignant psychosis which did not show rapid regression. Mental notes unfortunately are not complete, especially during the relapses of malaria. Nevertheless, from his autopsy report we may be sure that additional symptoms must have been present. However, it must be borne in mind that definitely psychotic patients having made a hospital adjustment do not show the characteristic mental reaction to malarial toxins that normal individuals of sound mind may.

While the brain was hardened throughout by an increase of neuroglia, still it is interesting to note that neurophagia took place in only a few cells. Evidently the nerve cells were not destroyed by the toxins, but rather suffered an intoxication therefrom. Cases of cerebral malaria that have come to autopsy are rare in the literature, although it is rather common to see cerebral malaria in highly malarious districts.

Case V showed the typical delirium, confusion and amnesia of a malarial toxic psychosis.

CASE V.—L. N., a white adult male, aged twenty-six years, with negative family history, was admitted, June 21, 1909. The patient had a common school education; had a normal earning capacity for one of his education; drank beer very moderately; denied venereal disease; always had a quiet reserved disposition.

He enlisted in the army and was sent to the Philippines, where he suffered his first attack of malaria in July, 1908. He was hospitalized from this time on. In November, 1908, the patient had delusions of persecution, acted irrationally and was melancholic. In January, 1909, he suffered greatly from malaria. Complete mental symptoms are not given in his history, although it was stated that he had "delirious symptoms." However, an amnesic period, while at the Manila Hospital in January, 1909, seems to have a marked psychotic symptom. The patient recalls only the ice baths, indicating that he must have been at that time much confused.

In February, 1909, he was transferred to Presidio Hospital,

California, and after one recurrence of fever and mental symptoms remained free from further attacks.

When admitted to St. Elizabeth's Hospital on June 21, 1909, examination brought out the following facts: Physically, the superficial lymph nodes were enlarged; there was increased splenic and liver dulness; weight was 154 pounds; height, 5 feet 7½ inches, well proportioned. Blood examination was not done, and the urine was negative. Mentally he is neat and tidy, and spends most of his time reading; is correctly oriented in all spheres; seems somewhat depressed; has good insight. From the patient's denial of hallucinations and delusions and irrational acts, it is very evident that he suffered from amnesia for a rather indefinite period of time, during which his malarial symptoms were at their height.

From the nurses' notes taken at frequent intervals during his stay at St. Elizabeth's Hospital, no psychotic symptoms can be gathered.

On November 12, 1909, he was entirely recovered. He recalled being mentally disturbed, but could not recall much that had gone on while he was at Manila. His trip across the Pacific was clear to him. On November 26, 1909, the patient was discharged as having recovered from his chronic malarial toxemia.

This patient from his history showed, notwithstanding the chronicity of the infection and amenability to treatment, quite the typical cerebral accompaniments, confusion and amnesia. Recurrence of mental symptoms bore a direct relation to a relapse of malaria with consequent liberation of toxins.

Case VI exhibits delirium, somatic delusions referable to the gastro-intestinal tract and amnesia, more or less complete.

CASE VI.—G. P. F., a white male adult, aged thirty-nine years, married, was admitted, September 30, 1913. He was very much depressed and somewhat mute.

The patient's family history was negative for nervous or mental diseases or alcoholism. His school and economic adjustments were normal. Due to the infidelity of his wife, he separated from her after ten years of rather pleasant married life.

About six weeks before admission to St. Elizabeth's Hospital he had an attack of malaria. He was ill for about two weeks. Following this he became delirious, excited and would not remain in bed. His admission note in September states that the patient was very dull and disinterested in routine procedures; lacked insight; was only approximately oriented; refused to eat his breakfast, saying the food was not good enough for him; he appeared restless at times, and wandered aimlessly about the ward.

Physically the patient was well developed and well nourished. The only positive finding was an area of tenderness localized in the extreme left hypochondrium.

On October 4, 1913, the patient said the reason why he could not eat was because he was constipated, but he refused to take a laxative. On October 7, 1913, the patient was only approximately oriented; he was emotionally flattened; his insight was very poor. He had delusions of persecution; he thought his food had human flesh in it; his memory was poor for remote and recent events. Numerous other mental tests showed him to be in very poor mental condition.

On October 9, 1913, after being transferred to another ward, he showed slight improvement. He was well oriented for time and person; was retarded in thought; he denied hallucinations and delusions; continually found fault.

On October 24 he again had delusions prohibiting him from eating; he had to be tube-fed until November 15; on November 18 he was quite confused.

On December 10 he had delusions regarding his bowels; was negativistic; tube-fed until January 31, 1917. At this time he began to take interest in his surroundings, worked a little, but was still delusional.

On February 17, 1914, the patient was coöperative, but still delusional. On March 4, 1914, the patient was quiet, agreeable and coöperative, and seemed to have improved greatly.

The urine and Wassermann reports were negative, and, although no blood examination for malarial parasites was done at the hospital we may accept the patient's account of his illness. On March 10, 1914, he states that he remembered having chills every other day, felt very sick and must have suffered about a week, during which time he took about 20 gr. of quinin a day. Since that time he cannot recall all the events that transpired. He admitted having persecutory ideas. He said he stopped using alcohol six months prior to his sickness. The patient has a partial amnesia for events that happened during his illness. At the time of this interview the patient was correctly oriented, denied hallucinations and delusions, and was in good physical condition.

The patient was discharged on April 27, 1914, as recovered.

The history of this case seems to exclude a dementia precox make-up, and from the age of onset makes a true precox psychosis doubtful. He evinced almost a complete amnesia from the time of onset of malaria until recovery from his psychosis. His delirious excited period was of shorter duration than some of the cases cited; however, his psychosis seems very closely allied to the attack of malaria, and whether or not malaria was the sole cause of the entire psychosis, at least it seems to have been the final factor.

Case VII has for its initial psychopathy confusion, amnesia, more or less complete, and the possibility of its being an early manifestation of paresis.

CASE VII.—C. E. B., a gunner's mate, first class, United States Navy, colored, aged thirty-two years, was admitted to St. Elizabeth's Hospital on October 9, 1908. His maternal grandfather died insane following sunstroke; his father used alcohol moderately. No other psychiatric determinants were present.

The patient had had the usual diseases of childhood; there was nothing of note in his early youth. He served twenty years in the navy, making good progress. He states that in 1890 he contracted malaria, and since that time he has had malaria every autumn. In 1895 he had two chancres, but no other symptoms from the infection.

In 1907 the patient had several attacks of malarial fever of short duration. About August, 1908, aboard ship, the patient acted in such a way that numerous complaints were carried to the surgeon. Finally he became morose, took no interest in his duties and wandered about the ship in a listless manner. His blood was negative for malarial parasites. He was transferred to the Norfolk Naval Hospital, September 15, 1908, where he was found totally disoriented, mute and seclusive. On September 16 the patient had a temperature of 102° F. Blood examination showed malarial parasites, and quinin (10 gr. every four hours) was given. The patient had a retrospective falsification of memory. The symptoms remained the same throughout the month of September. On October 6, 1908, his temperature was normal. He showed little improvement mentally, was disoriented; had hallucinations of alligators and people dressed in fancy costumes; did not remember how or when he came to the hospital. The patient states that he came to himself after being in the Norfolk Hospital for some time.

Physically, when admitted to St. Elizabeth's Hospital, October 9, 1908, he weighed 148 pounds, his height was 5 feet 8 inches and he was fairly well nourished. His muscles were somewhat flabby, and he had a well-marked stomatitis. There were no nervous symptoms other than slight tremor of the extended fingers.

On October 13, 1908, the patient appeared apathetic and confused. His consciousness was clouded and he was imperfectly oriented in all spheres. His attention was held with difficulty, and his memory for recent events was poor. There was almost a complete amnesia for what happened from the time of his transfer from the Idaho to the Naval Hospital at Norfolk until he was transferred here. Delusions and hallucinations were present at the Naval Hospital, but he denies their presence now. Reasoning and judgment were impaired. He lacked insight. At this time, while taking quinin, the patient had frontal headaches and insomnia, slight rise in temperature and bodies doubtfully resembling plasmodia in his blood. Urinalysis was negative. On October 30, 1908, his mental condition had improved very much. He was oriented in most respects; comprehended questions and his replies were fairly

prompt, coherent and relevant. There was still an amnesia for most of what occurred at the Naval Hospital. Since his arrival here he has been free from hallucinations and no delusions could be detected. Shortly after admission he began to take an interest in his environment, headaches disappeared and the patient gained weight.

On November 28, 1908, he continued to improve and had ground parole. December 31, 1908, the patient showed no evidence of mental disorder but still lacked insight. Diplopia formerly present had disappeared.

On February 3, 1909, the patient was given the privilege of a short visit. The patient got along well and was discharged on August 10, 1909, as recovered.

Although general paresis cannot be entirely ruled out in this case, still we have no laboratory findings indicative of that disease (White). While on the other hand, his malarial infection and recovery seem to bear a very direct relation to the onset of and the recovery from mental symptoms, this patient's history for the following ten years might have brought out more exact knowledge of his psychosis.

It appears that we have to deal with a normal adult negro who contracted malaria many years ago; suffered from numerous attacks, but in 1908 he developed a condition resembling dementia pre-cox, and closely associated with a relapse of malaria probably more severe than usual. Associated with this attack was a very definite amnesia which lifted after quinin medication. Mention was made of diplopia which cleared up with the treatment. This seems to indicate that the toxic infection found the central nervous system a point of attack, and it seems not unreasonable that it could also account for the mental symptoms elicited. Paresis also must be borne in mind.

If the observations of Wagner-Jauregg⁵¹ and others⁵² upon the therapeutic effect of malarial toxic infection in paresis are of value, then it may have been fortunate for this patient who may have had paresis to have malaria added to this infection.

Symptomatology in General. The symptomatology of necessity must be varied, and in addition it is of great value to know the patient himself. This can be clearly seen from a review of the literature of the subject; one observer finds depression, another maniac outbreaks, others a short-lived delirium and so forth. The determining factor, to a large extent, is then the individual reaction of the patient.

The patient is confused and is oriented, and at this time shows a tendency to his individual reaction type, a precox form, a catatonis or maniac form and so forth. (Torquato Tasso was considered a subject of malarial melancholia.) A fear reaction appears to be fundamental in all cases.

Due to a lack of attention during the delirium, or rather because of a dissipated attention, the patient awakes from his delirium or confusional state with an amnesia for all that has happened. Complete amnesia is not found in all cases, but in all cases there is at least some impairment of memory. Since the amnesia is conditioned by delirium, it is dependent upon the depth of delirium for its completeness. In chronic malaria the mental picture, while less distinct, is fundamentally on the same basis as in the acute outbreaks. At times a reaction similar to the acute psychosis is seen, but most frequently there results a malarial neurasthenia. The psychosis often acts as a malarial equivalent, and in this case an ephemeral mental confusion takes the place of an attack; that is to say, there may not be an appreciable rise in temperature nor the usual signs of an attack, but instead a short-lived mental confusion may represent the entire symptomatic picture. These short attacks of mental confusion can hardly be designated a psychosis, but when occurring frequently so incapacitate the patient that they approach that of a true psychosis.

Summary and Conclusions. That there is a malarial psychosis can be definitely stated, but on account of many factors, its physiognomy is of necessity varied.

Of the determinants giving a diverse mental picture may be mentioned: Alcohol, severity of the attack *per se*, age of the patient at the onset of the malarial attack, even the acuteness or chronicity of the disease, and lastly, hereditary taint. A few manifestations, however, are quite constant, such as initial mental confusion, oniric delirium and more or less complete delirium.

The symptoms of a malarial intoxication with its oniric delirium resemble those of other toxic infectious psychoses. They are modified somewhat by hepatorenal insufficiency.

Although patients with a malarial psychosis are frequently found to have been alcoholic at the time of onset of the disease, and although malarial patients are capable of easy alcoholization, alcoholism has not been found to be a necessary accompaniment.

Arabs, who were not as a class alcoholic, whenever they developed a malarial psychosis, lacked the initial delirium, while Europeans with an alcoholic taint, on the contrary, always developed an initial delirium. This is so constant that several observers have taken it as an indication of alcoholism.

The severity of the malarial attack in a susceptible individual is on a quantitative basis, and so determines his reaction. With a florid attack the quantity of malarial toxin is greatly in excess of that of a mild attack, so that in the former case we would expect greater mental aberrations than in the latter.

Depression has been most frequently observed in children.

Jews as a race tend to develop a catatonic reaction.

The mental symptoms appearing with the first infection of

malaria are generally: (1) Delirium, which is intermittent, not very well sustained, rather monotonous and not expansive; (2) confusion with dream delirium, followed by amnesia dating from the onset of delirium and varying in its completeness.

In chronic malaria the individual attacks are less severe, less noticeable, generally taking the nature of a depressed mental state, and gradually shading into a neurasthenic or hysteroneurotic condition.

A nervous system with hereditary taint is suitable soil for the development of a malarial psychosis. This and the malarial tox-infection are in themselves capable of setting up mental aberrations in a patient, but probably as often as not alcoholism is also present. This in turn aids the malarial intoxication and results in a mental upset.

Twelve cases of malaria in patients suffering from several different types of psychoses (non-organic) did not show added psychotic symptoms. The failure to elicit mental phenomena due to malarial intoxication, however, does not detract from the hereditary factor in malarial psychoses. Old hospital cases on "back wards," not subject to the careful scrutiny and study that newer and more hopeful cases demand, might easily develop some few new mental symptoms under a malarial attack and have these overlooked. Again, in non-organic cases already on a low mental level, living the well-protected life of an institution, malarial infection might conceivably be insufficient to bring out aberrant mental reactions, such reactions as might be termed significant of a higher mental state bearing the brunt of a toxic infection.

In one case herewith reported, paresis could not be definitely ruled out, although the tendency was to believe that his mental upset was due to malaria. In this connection it is interesting to note that Pilez,⁵³ using von Wagner's treatment for general paralysis, occasionally noticed acoustic hallucinations, ideas of persecution, delirious and catatonic states in those subjects infected with malaria. All their symptoms disappeared when quinin was given.

Pathologically, of outstanding importance is the plugging of small arterioles and capillaries in the brain and spinal cord. The thrombosis or embolism in perforating arterioles, if not fatal, causes the most serious consequences. This tendency to thrombosis and embolism partly explains the presence of almost any of the topographical neurological syndromes noted occasionally in the course of malaria. Most interesting, as well as most rare, is the development of motor aphasia, due to the blocking of capillaries surrounding Broca's area.

The delirium is well explained by the marked hyperemia of the pia vessels, subarachnoid perivascular and pericellular spaces, and plugging leading to punctiform hemorrhages.

The development of coma is found to be due, aside from such preëxisting conditions as anemia, cachexia, physical or mental fatigue, the puerperium, insolation and alcoholism, to the number of parasites present, the amount of toxin secreted and, most of all, to localization of the toxi-infection in the brain.

In cerebral malaria the symptoms may simulate any brain disease, but the mental symptoms are not commensurate with the cerebral trauma due to the parasites *per se*. They are exaggerated, and point to a cerebral intoxication.

Neuritides, neuralgias, hyperalgesia, headaches, and acute hyperpyrexial attacks are but indications of the effect of malarial toxins on peripheral and central neurones.

Amnesia of malarial origin is conditioned by the lack of attention during and after the initial delirium, and is of varying grades. One case studied had an amnesia for six months.

As aforementioned there is a difference of opinion on the exact clinical picture exhibited in a malarial psychosis. From the first there is a bradypsychia which observers have found to progress to a frank depression. Maniacal outbreaks, not frequently observed, can only be attributed to a constitutional predisposition. Depression is always noted in varying degrees in those long affected with a malarial infection. One writer explained this from the fact that most of his cases of malarial psychosis were in women, and they are the more given to depression. Racially speaking, Jews, when affected with malaria, have been found prone to a catatonic development. Several observers have noted that the malarial mental confusion has, for its essential character, the accompaniment of certain symptoms which evolve toward dementia precox catatonica. In my first case of malarial psychosis it was the consensus of opinion that the patient was a case of catatonic dementia precox. Each consultant, however, expressed some doubt as to the diagnosis, and was wont to give malaria as the possible cause of the development of the psychosis.

Malaria over a period of years, with a history of rather frequent outbreaks, is capable of bringing on a marked neurasthenic condition. Aside from the possible psychic effect of a chronic debilitating infection, malaria attacks the hemopoietic function and vitiates it at its source, thus making the patient a fit subject for neurasthenia.

Epilepsy and hysteria, according to good observers, are caused by malaria, and in preëxisting conditions the infection serves to aggravate the symptoms of both.

BIBLIOGRAPHY.

1. von Ezdorf, R. H.: Reference Handbook of the Medical Sciences, 3d ed., New York, Wm. Wood & Co., 1916, 6, 220.
2. Jelliffe, Smith Ely and White, William A.: Diseases of the Nervous System, 2d ed., Philadelphia, Lea & Febiger, 1917, p. 838.

3. Skliar, N.: Ueber die Psychosen bei den Infektions-krankheiten, insbesondere beim Flecktyphus und Rekurrens, *Psychiat. u. Neurologie*, 1922, 52, 21.
4. Papastratigakis, G.: La confusion mentale palustre, *l'Encephale*, 1922, 17, 105.
5. Régis, E.: Psychoneuroses et psychoses du paludisme, *Bull. méd.*, 1905, 19, 615. Dr. Ponty, quoted by Régis, loc. cit.
6. Lecler, J.: Contribution a l'étude des états délirants au cours du paludisme, Paris, Jouve, 1920. (Abstract by Vinchon, J.: *L'Encephale*, 1921, 16, 169.)
7. Folly: Le Médecin-major: Les paludéens délirants; Rôle de l'alcoolisme, *La caducée*, 1905, 5, 313.
8. Neer, C. S.: Comatose Pernicious Malaria, *Jour. Am. Med. Assn.*, 1908, 50, 1890.
9. Tresidder, A. G.: A Case of Malarial Coma Lasting Forty-six Hours: Recovery, *Lancet*, 1914, 1, 891.
10. Quaipe, W. T.: A Case of Cerebral Malaria; Recovery after Forty-eight Hours Unconsciousness, *Lancet*, 1912, 1, 74.
11. Graham, E. N.: Unusual Manifestations of Malaria, *Jour. Trop. Med.* 1909, 12, 151.
12. Knowles, R.: Malaria Coma with Subsequent Aphasia, *Indian Med. Gaz.* 1911, 10, 303.
13. Thomson, Wm. H.: A Treatise on Clinical Medicine, Philadelphia, W. B. Saunders & Co., 1914, p. 212.
14. Ascoli, V.: La malaria, Torino, 1915.
15. Von Krafft-Ebbing: Nothnagel's Encyclopedia of Practical Medicine, American edition, 1905.
16. Manson: Ibid.
17. Segard: Ibid.
18. Pasmanik: Ueber malaria Psychosen, *Wien. med. Wehnschr.*, 1897, 47, 517.
19. Gehrenstein, S. S.: Malarial Psychoses, *Vrach. Gaz.*, 1906, 13, 919.
20. Chavigny, M.: Complications nerveuses et mentales du paludisme, *l'Encephale*, 1912, 1, 387.
21. Parot, A., and Gutmann, R. A.: Les psychoses du paludisme, *Paris méd.*, 1917, 24, 518.
22. Parot, A., and Gutmann, R. A.: Les psychoses du paludisme; formes clinique, *Paris méd.*, 1918, 27, 241.
23. Forrester, A. T. W.: Malaria and Insanity, *Lancet*, 1920, 1, 16.
24. Manson, Sir Patrick: Tropical Diseases, London, 7th ed., 1921.
25. de Brun, M. H.: l'Amnesie paludisme, *Presse méd.*, 1917, 25, 625.
26. Carlill, H.: Korsakow's Psychosis in Association with Malaria, *Lancet*, 1917, 1, 648.
27. Goodhart, S. P.: Amnesias of Tobacco and of Malarial Origin, *Jour. Am. Med. Assn.*, 1913, 61, 2297.
28. Marchiafava and Bignami: Malaria, New York, 1900. Cited by Deaderick, W. H.: The Pathogenesis of Pernicious Malaria, *Med. Rec.*, 1908, 74, 140.
29. Mannaberg: Malarial Diseases, Philadelphia, 1905. Cited by Deaderick, W. H.: The Pathogenesis of Pernicious Malaria, *Med. Rec.*, 1908, 74, 140.
30. Weingartner: Autopsy Reports of Two Cases of Malaria, *Ztschr. f. d. ges. Neurol.*, 1921, 24, 13.
31. Ewing, James: Contribution to the Pathological Anatomy of Malaria Fever, *Jour. Exper. Med.*, 1902, 6, 119.
32. Jones, D. W. C.: A Note on Segmental Hyperalgesia in Malaria, *Lancet*, 1919, 2, 283.
33. Rao, S. S.: Motor Aphasia Due to Malaria, *Brit. Med. Jour.*, 1912, 1, 1240.
34. Dec, P.: Malarial Fever with Aphasia, *Indian Med. Gaz.*, 1906, 41, 363.
35. Browne-Mason, H.: Malaria (Malignant Tertian), a Case Complicated with Temporary Aphasia, *Jour. Roy. Army Med. Corps*, London, 1905, 4, 648.
36. Gillot: l'Aphasie paludéenne, *Bull. méd. d'Algerie*, 1904, 15, 597.
37. Milner, C. E. H.: The Relation Between Heat Stroke and Malignant Malaria, *Brit. Med. Jour.*, 1918, 1, 638.
38. Blin and Kerneis: Case of Anterior Spinal General Paralysis in a Soldier Due to Malaria, *La Caducée*, August, 1916; Abstract, *Med. Rec.*, 1916, 90, 519.
39. Stedman, E. C.: An Unusual Manifestation of Malaria, *Jour. Am. Med. Assn.*, 1905, 44, 1685.
40. de Brun, M. H.: Note sur le tremblement paludéen, *Bull. de l'Acad. de méd.*, 1918, 79, 269.
41. Jourdan, M.: Du tremblement palustre, *Presse méd.*, 1906, 14, 518.

42. Fornaca, Giacinto: Tremore da malaria, Roma, 1907, 8, 15.
43. Pope, C.: Chronic Malarial Cachexia and its Relation to Neurasthenoid Conditions, Boston Med. and Surg. Jour., 1914, 170, 193.
44. Atkinson, J. F.: Malaria and Afterwards, Indian Med. Rec., 1913, 33, 177.
45. Musgrave, W. E.: A Case of Masked Tertian Fever with Marked Mental and Nervous Manifestations and with Unusually Few Parasites in the Peripheral Circulation, Bull. Manila Med. Soc., 1911, 3, 28.
46. Hare, Francis: Pathological Variations of Physiological Vasomotor Action, with Special Reference to the Malarial Paroxysmal Neuroses, Practitioner, 1905, 75, 150.
47. Marandon de Montyel, E.: Revue de méd., 1889, 19, 921.
48. Regnault: Hysterie et impaludisme, Marseille méd., 1890, 27, 337.
49. Roux: Hysterie chez un paludéen, La Caducée, 1902, 2, 47.
50. Marandon de Montyel, E.: Rapports de l'hysterie et de l'impaludisme, Presse méd., 1900, 2, 281.
51. Prof. Dr. Wagner-Jauregg: Treatment of General Paresis by Inoculation of Malaria, Jour. Nerv. and Ment. Dis., 1922, 55, 369.
52. Delgado, H. F.: Treatment of Paresis by Inoculation with Malaria, Jour. Nerv. and Ment. Dis., 1922, 55, 376.
53. Pilcz, A.: von Wagner's New Treatment of General Paralysis, Lancet, 1923, 1, 19.

THE RELATION OF FUNGI IMPERFECTI TO DIARRHEAL CONDITIONS.

BY MOYER S. FLEISHER, M.D.,

AND

M. WACHOWIAK, M.D.,

ST. LOUIS, MO.

(From the Department of Bacteriology and Hygiene, St. Louis University, School of Medicine.)

ABOUT two years ago we became interested in the problem of the occurrence of fungi* in the intestinal canal of human beings, and began a study of the stools of normal persons, as well as those of persons in hospitals, for condition other than gastrointestinal disturbances. However, we were soon led to an interest in cases

* We use the terms fungi imperfecti, oöspora, monilia, monilia-like organisms and common yeasts throughout our article in a somewhat loose sense, since we have as yet not definitely placed many of the organisms isolated, and since we are as yet undetermined as to which of the numerous botanical or medical classifications to follow. However, when we speak of common yeasts we refer to organisms showing a yeast-like form which would be classed as ascomycetes (having an ascospore sac), and especially organisms which fall outside the group of fungi imperfecti. By fungi imperfecti we mean organisms which do not belong either among the ascomycetes or phycomycetes, and in which reduction takes place by means of conidia produced on conidiophores which are either enclosed in perithecia placed on disks or are unprotected. The oöspora, monilia and monilia-like organisms, we believe, all belong to the family Oösporaceæ, Saccardo 1886, and show septate hyphæ; conidia are produced on simple carriers and conidia appear in rows. In the ones we have called oöspora there is a tendency for the hyphæ to break up into the conidia. The monilia show a tendency to produce conidia at the ends of the hyphæ, which do not break up as in the case of the oöspora, and there is a tendency toward the appearance of the conidia in clusters. The monilia-like organisms are very similar to the monilia, but show certain minor differences.

in which there was evidence of intestinal disturbance, and we have now for some time been studying cases in which there existed a chronic diarrhea. Our studies have not lead to positive conclusions, but so much material has been collected that we cannot escape the belief that a relationship exists between certain types of fungi imperfecti and some diarrheal conditions. We publish this article, therefore, with the hope that further studies may be made in this direction, and that with the accumulation of evidence this relationship may be more sharply defined.

Fungi have been considered by a number of individuals to be the causative agent of specific intestinal disturbances, and in the past ten years or so this relationship has been especially stressed in connection with tropical sprue. We shall not attempt to review here the literature concerning the etiology of this disease, because it has recently been fully covered in an article by Bastedo and Famulener.¹ Suffice it to state that Ashford,² investigating a large number of cases of sprue in Porto Rico, came to the conclusion that a specific organism, to which he gave the name *Monilia psilosis*, was the causative agent. Many observers, especially Castellani,³ do not agree with his conclusions. However, in recent years Castellani⁴ has somewhat modified his position, and in a more recent publication states that, while he cannot definitely deny the possibility that fungi imperfecti may have something to do with sprue, he does not believe the *Monilia psilosis* of Ashford to be the only organism which might be associated with sprue. Also, that if fungi imperfecti are concerned in this disease there are several different varieties which may possibly be causative agents. Of such, he mentions about seven species of both monilia and oïdia.

Therefore, at the present time the exact relationship between monilia and sprue is not undisputed, and future and further work will be necessary in order to clear up this problem. We believe, however, that the finding of monilia-like organisms in the blood of a chronic case of sprue from Korea (which we⁵ reported about a year ago), and the confirmation of this finding by Ashford in cases in Porto Rico, which fact he was so kind as to communicate to us, makes almost certain the necessity of relating some of the disturbances in sprue to this type of organism.

It is apparent that one cannot put these findings lightly aside; certainly it does not necessarily follow because an organism is present in the blood of a patient that such organism must bear a causal relationship to the disease. But it is equally certain that if an organism is very constantly found in the stool in a condition in which diarrhea is a cardinal symptom, and the same organism when administered by mouth will produce diarrhea in animals, and, finally, if the same organism can be found in the blood of the patient, as well as in the blood of the animal which was fed, then we must give most careful consideration to the role of that organism in that disease.

Probably the most telling arguments which have been raised against the relation of monilia or similar organisms to sprue have been the findings in cases of diarrhea and also in normal individuals. Thus, Ashford,⁶ from Porto Rico, reported finding *Monilia psilosis* in 17 per cent of cases not sprue, but showing gastrointestinal disturbances, and 3 per cent of normal individuals. Dold,⁷ in China, found monilia or related organism in 16 per cent of cases with diarrhea which were not sprue and similar organisms in 7.5 per cent of normal stools. Castellani also found monilia or oïdia in the stools of normal individuals, as well as in the stools of diarrheal cases, not sprue.

It is interesting to note that both Ashford and Dold found fungi more frequently in the stools of diarrheal cases which were not sprue than in the stools of normal individuals. It is, therefore, suggested that either the fungi are in some way related to the diarrheal conditions or that, as a result of abnormal conditions in the intestinal tract, the fungi are better able to gain a footing and persist there.

In connection then with these observations, we wish to report here upon a series of 32 cases which we have studied culturally, in 20 of which fungi have been isolated from the stool and, in some cases, from the blood.

The 20 cases in which fungi imperfecti were found can be divided into several groups: (1) A series of cases which were definitely diagnosed as tropical sprue, 7 having originated in Korea and 1 in Mexico; (2) a group of cases in which there was either a chronic diarrheal condition or an ill-defined gastrointestinal disturbance; (3) a group of cases in which there was an acute diarrheal condition but which, however, usually cleared up in a brief time.

The first case of sprue has already been referred to in our earlier publication, and we give here a brief abstract of the case as well as the findings.

CASE I.—Dr. R. M. W., while in Korea, developed sprue. He returned to this country during the year 1922, and was put in touch with us through the kindness of Dr. J. E. Cook. When we saw him he complained of a sensation of distention, flatulency, indigestion and mild diarrhea; he slept poorly and was irritable. His general appearance was quite fair; he did not show emaciation. We obtained a specimen of stool and isolated a yeast-like organism. In addition, in a blood culture taken at the same time we obtained an organism identical with that found in the stool. In this case we find the organisms both in the blood and in the stool. The organism has not as yet been specifically identified, but it is either a monilia or a monilia-like organism.

CASE II.—E. W., a patient of Dr. A. Taussig, had lived in Mexico for forty years. His health was good until June, 1922, when he had

a violent attack of vomiting with diarrhea; this lasted a week and was followed by complete recovery, except for some remaining weakness. In July diarrhea returned and continued intermittently until October. Then he began to have a sore mouth; gums, inner aspect of lips and especially the tongue were reddened, swollen and painful, so that he could hardly eat. This condition remained severe for three weeks, but did not entirely cease until the end of November. For several months the diarrhea was persistent; bowel movements massive, clay-colored, often foamy, usually extremely foul and occurring more frequently at night than during the day.

We isolated a monilia from the stool of this patient, but were unable to find a similar organism in the blood. The patient was treated with a vaccine, prepared from the organism, and showed improvement which, however, lasted only a few months. Eventually he left the city and died, according to the report we received, of anemia and asthenia.

The remaining 4 cases in this group (Cases III, IV, V and VI) were persons suffering from sprue acquired in Korea, and from them we obtained only specimens of stool. The disease was in a chronic form, and the patients had all been invalided to this country to recuperate. The specimens were sent to us through the kindness of Dr. E. M. Wilson. In 3 of these cases we isolated from the feces organisms similar to those found in the first case, and in the fourth we found an oöspora in the stool.

Thus, in all 6 cases of tropical sprue we were able to isolate fungi imperfecti from the feces, and in 1 of these cases the same organism was found in the blood.

In addition, we examined stools from 2 quiescent cases of sprue which had, like the last 4, originated in Korea, but we were unable to find monilia-like organisms in the specimens. They were both cases which did not show any symptoms at the time the specimens were taken, and the stools were certainly not sprue-like in character. However, in 75 per cent of the cases of sprue we found fungi imperfecti in the stools.

In the second group the first 2 cases, both chronic diarrheas, we are able to report through the kindness of Dr. J. W. Larimore. The abstracts of the histories are given here.

CASE VII.—M. W. complained of diarrhea since January, 1922, which was worse and constant since June, 1922. Stools: Three movements daily, mostly in the morning after 5.30 A.M.; thin and watery and very foul; no foam, mucus or blood; "rush" movements follow large meals. Loss of weight from 160 to 120 pounds in eight months. Tongue very sore. Physical examination showed anemia malnutrition, dental caries, tongue red and fissured. Gastric anal-

ysis showed achlorhydria. A monilia was isolated from the stool, and a vaccine prepared from this organism. After administration of the vaccine the condition of the bowels was much improved to only slight frequency and to near normal form and consistency. The patient otherwise remained about stationary, with slight increase in hemoglobin.

CASE VIII.—M. S. complained of frequent stools and abdominal discomfort for five to six years. Stools: Two to four movements daily, often induced by eating, following in thirty minutes; thin, mushy, voluminous and foul. Some irritation of the anus. Weight: Stationary at 146 pounds. Examination showed nothing notable. Stool analysis: Dark brown, mushy, no gas, foam, mucus or blood. An oöspora was isolated from the stool and the vaccine prepared. Improvement of bowel condition was definite during and following vaccine treatment with restoration of normal character of stool, but movements continued twice daily and were increased with excitement.

CASE IX.—Mrs. L. W., a patient of Dr. M. Wachowiak, had diarrhea for eight months. It came on rather suddenly, six to eight or even ten stools a day, with no relief as a result of medical treatment; sugar diet aggravated condition. An oöspora, possibly similar to that called *Oidium asteroides* by Castellani, was isolated from the stool and from the blood. The patient was treated with the vaccine prepared from the organism and the diarrhea cleared up entirely. Her condition has remained satisfactory for a period of a year.

CASE X.—F. R. R., a patient of Dr. W. Engelbach, began to have intestinal trouble in November, 1917, while the patient was in the army in France, with the appearance of mucus in the stool. This condition persisted until the spring of 1918, at which time there was an increase in the number of stools to eight to ten a day. Some loss of weight occurred, the exact amount not known, with the appearance of general weakness, and at about this time flatulency appeared. The condition persisted with exacerbations and remissions. The patient noticed that there was a definite aggravation following exercise. There was a fluctuation in the number of stools a day, varying from four and five to eight to ten. Monilia-like organisms were found in the stool but not in the blood of this case; a vaccine was prepared and, following the administration, there was marked improvement, although the frequency of bowel movements was not quite restored to normal. This improvement has lasted for about eight months, and the patient is better than at any time since the disease started.

Cases XI and XII have been reported in our earlier communication.

CASE XI.—E. W., a patient of Dr. C. F. Wilhelmj, was located during the war at Camp MacArthur, where he came in contact with soldiers, who had previously served in the tropics, and some of whom were suffering with diarrhea. He did not have diarrhea while at Camp MacArthur, but after he was transferred he developed an attack of diarrhea of brief duration; however, intermittently thereafter this diarrheal condition lasted up to the time he was seen in the summer of 1922. His weight had fallen from 153 to 112 pounds. He did not show any stomatitis at any time; his stools were liquid and not sprue-like in character. Cultures of the feces and blood both showed the presence of a monilia-like organism.

CASE XII.—B. R. was a patient at the Jewish Hospital of St. Louis, whom we were able to examine through the kindness of the physician of the medical service of that hospital. In 1921 he was operated upon for appendicitis. His convalescence was slow and he had considerable abdominal discomfort for many months afterward. Finally, in January, 1922, what was apparently an abscess in the abdominal wall was opened; the abscess cavity, from all appearances, communicated with a walled-off peritoneal abscess. This continued to discharge and failed to heal. While the patient suffered with intermittent and rather mild diarrhea, blood being present in the stool, at no time was the diarrhea of serious moment. Monilia-like organisms were found in the stool, in the discharge from the fistula and in the blood.

CASE XIII.—C. F., a patient on the service of Dr. R. A. Kinsella at the Barnes Hospital, had a chronic infectious arthritis, involving several joints, and also intermittent diarrhea. Frequently there was a discharge from the rectum, which was purulent. On proctoscopical examination a simple polyp was formed. In this case a monilia-like organism was found in the stool, but not in the blood. At the time we did not realize the possible significance of this finding and no vaccine was administered, this being at a rather early period in the course of our work.

CASE XIV.—B. K. had been under observation of Dr. J. E. Cook for some years, with intermittent diarrhea of varying severity, showing from time to time blood and mucus in the stool, without, however, any very marked loss in weight or distinct discomfort. In this case we found a monilia-like organism in the stool, but no vaccine was used.

CASE XV.—M. S., a patient of Dr. A. J. Kotkis, had had intermittent attacks of diarrhea for four years, with from two to six

bowel movements a day. Sometimes these attacks came on at night, but they were irregular in the time of appearance. At times the attacks were mild and of short duration, again they might be severe and persistent. No type of diet or medicinal treatment seemed to have controlled or modified the condition. A monilia was found in the stool and the patient was treated with a vaccine prepared from the organism, and only a slight beneficial effect was noted.

The third group represents a series of cases in which there was mostly an acute diarrhea, usually with spontaneous recovery, and in 1 case ending in death.

CASE XVI.—F. T., a patient of Dr. Larimore, had a sudden "spell," after which he was unable to walk for eight weeks. Eight weeks before he was seen he developed a severe diarrhea after being constipated all his life; he had poor control of the rectum during these weeks. Loss of weight from 180 to 143 pounds in five months. The stool was semifluid and gassy. Gastric analysis showed achlorhydria. Here a monilia-like organism was isolated from the stool, but, as the patient died, no vaccine treatment was administered.

CASE XVII.—C. B., a patient of Drs. Ehrenfest and Sale, was operated upon, December 22, 1922, for fibromyoma of the uterus, and a hysterectomy was performed. December 23 or 24 the patient began to have severe diarrheal attacks, the number of stools varying between eight and eighteen. This continued until December 30, and was associated with nausea and vomiting. The diarrhea subsided automatically without any particular specific treatment. A monilia-like organism was isolated from the stool of this case, which, as stated, recovered spontaneously, so that no vaccine treatment was called for.

CASE XVIII.—M. B. was a patient of Drs. S. Simon and J. E. Cook. Seven days before admission to the hospital there had been a sudden onset of abdominal cramps, chills and fever of 103° , with ten to twelve loose stools, principally blood and mucus. This was associated with abdominal discomfort. Nothing in particular was evident on physical examination. No particular cause for diarrhea was evident during the stay in hospital. The number of stools became approximately normal after about eight to ten days. A true monilia was isolated from the stool in this case.

In 2 additional cases (XIX and XX) stools were sent to us. No history beyond the diagnosis of a chronic diarrhea of unknown origin was available. Both showed oöspora in the stools.

We then have here a series of 20 cases, including 6 of sprue in which there was a diarrhea, and in each one of them there was isolated from the stool a monilia, monilia-like organism or an oöspora. It should be mentioned that in all these cases amebic or bacillary dysentery and tuberculosis have been excluded in as far as was possible; that in all, therefore, the etiological factor was uncertain or unknown.

In 4 other cases, in which a diagnosis of either amebic dysentery or enteric tuberculosis was eventually made, we found no monilia in the stool; but in 1 of these a common yeast was found.

In 12 additional cases in which diarrhea was a prominent symptom, but in which no definite diagnosis concerning the causative factor could be made, we found no fungi imperfecti.

Thus, in 32 cases of diarrhea in which no specific diagnosis determining the cause of the gastrointestinal disturbance was made, or in which sprue was diagnosed, we found monilia or similar organisms in the feces in 62.5 per cent of the cases. If we omit the 8 cases of sprue and consider only the 24 cases of diarrhea of undetermined origin the fungi imperfecti were present in 58 per cent of the stools of this group.

Discussion. There naturally arises the question whether we are justified in assigning any etiological relation in these diarrheas to the fungi imperfecti.

In the first place: Is there any evidence that these organisms are associated with the production of gastrointestinal irritation leading to diarrhea? This can be answered in the affirmative, since in rabbits fed with certain of these organisms (monilia, monilia-like or oöspora) a diarrhea was produced with the appearance of the organism in the feces. The organisms were found in the blood of some of the animals, and at times at autopsy; lesions were also present in the liver and lungs from which we were able to isolate the organism. In a number of cases the fed rabbits died. We should state, however, that we have not as yet tested all of these organisms in animal experiments, but are at present carrying out such experiments.

Aside from this experimental evidence, it is generally recognized that yeasts act as cathartics; however, if the common yeasts are fed to animals they rapidly disappear from the stool; on the other hand, if these fungi imperfecti are fed to rabbits they persist in the stool for considerable periods. Their effect then is apparently more than merely a transitory one due to the introduction by feeding. Anderson⁸ has shown that common yeasts fed to man also rapidly disappeared from the stool, but *Monilia psilosis* persisted in the stool for a long time. There is, therefore, apparently a difference between the relationship of wild yeasts to the mammalian organism and the relationship of at least some of these fungi imperfecti to the same organism.

There still remains the question which will naturally arise in every mind: To what extent do we find organism similar to these mentioned above in the stools of normal individuals? As we have stated above, Ashford, Castellani and Dold have all found similar organisms in the stools of normal individuals. Anderson some years ago investigated the fungi occurring in the stools of normal individuals and found yeasts or yeast-like organisms in 47 per cent of the ninety-eight normal stools examined. In individuals with diarrhea he found similar organisms in 46 per cent out of thirty-seven examined. However, it is not clear from his reports how many of the organisms found were of the monilia or oöspora type; apparently most of them were of the common yeast type, and only about 4 seem to have been either monilia or oöspora. His results are, therefore, not directly available toward clarifying this point.

We have examined the stools of a number of normal individuals, and found in a first series common yeasts or fungi imperfecti in 38.5 per cent of sixty-six stools. The majority of these, however, are neither monilia or oöspora; in only 2 cases were monilia-like organisms isolated, and in 1 additional case an oöspora was found. We have recently examined a second series of twenty-four normal stools, and here 1 monilia and 5 oöspora, resembling these found in the diarrheal stools, were found. Thus, in ninety stools from normal individuals we find these fungi imperfecti in only 10 per cent of the stools. From the evidence of the investigations of others as well as our own work, it seems that organisms of this type are occasionally found in the stool of normal individuals, but by no means as frequently as in the stools of individuals with diarrhea.

Furthermore, we believe that the finding of fungi imperfecti in the blood in certain of these cases adds very materially to the weight of the evidence. It is true that they were not found in the blood in all cases; but, of course, in many other diseases, where we know a bacteremia exists, we do not constantly find organisms in the blood cultures. It is possible that our technic is as yet imperfect, and that with improvement in this respect our findings of these organisms in the blood may become more frequent.

Nevertheless we have found fungi imperfecti in the blood stream in 4 of our 20 positive cases—1 of sprue and 3 of chronic diarrhea. In 3 cases there were monilia-like organisms and in the fourth an oöspora. It seems hardly plausible that an organism, present in the intestinal canal, capable of causing gastrointestinal disturbance and also present in the blood stream, should not have some relationship to the patient's condition.

Summary. If then we summarize the evidence brought together here it runs somewhat as follows:

1. In a series of cases in which diarrhea was a prominent, if not the most prominent symptom, we have been able to demonstrate in the stools the presence of fungi, monilia or similar organisms in

62.5 per cent of these cases. In some of these cases identical organisms have been demonstrated in the blood stream.

2. A number of these organisms have been fed to rabbits, and in such animals they have produced diarrhea—in some cases even death. In some of these animals the organisms have been recovered from the blood and from lesions in the internal organs.

3. *Monilia* or similar organisms are to be found in the stools of normal individuals in a small percentage of cases, in a much smaller percentage than where a diarrhea exists. Relatively in normal individuals the occurrence of these fungi in the feces is infrequent.

4. Are we then justified in considering these organisms as having any bearing upon the diarrheas in these cases? We are at present inclined to believe that in those specific conditions, as in sprue—in which fungi imperfecti are generally found (we found them in 75 per cent of our cases)—some causal relation exists between the organism and the symptoms. We believe that our finding, namely that the organism may be present in the blood stream, very materially strengthens this viewpoint. We believe that it will be difficult to deny a relationship between the symptoms of a patient and an organism found in both stool and blood of a case of diarrhea not diagnosed as sprue.

5. While we realize the possible fallacy in attempting to base any conclusions regarding etiology upon the results of vaccine therapy, nevertheless the improvement showed in certain of these cases following vaccine therapy, suggests a possible relationship existing between these fungi and the disease. Our results do not warrant us in going any further than this, but we suspect that in many cases, where there exists a chronic diarrhea which cannot be explained on any other basis, organisms of this type may be factors. We wish to make clear that, of course, we do not think nor wish to suggest that fungi play a part in all diarrheas, even though no causal agent may be evident.

6. Finally, we present this series of cases, our results and our tentative conclusions simply as a suggestion for further investigation in this field.

NOTE.—A further study, since this article went to press, of the so-called *monilia*-like organisms has demonstrated that they should be classed as *monilia*.

BIBLIOGRAPHY.

1. Bastedo and Famulener: *Jour. Am. Med. Assn.*, 1924, 81, 2102.
2. Ashford: *AM. JOUR. MED. SCI.*, 1915, 150, 680; *Ibid.*, 1917, 154, 157.
3. Castellani: *Brit. Med. Jour.*, 1921, 1, 338; *Jour. Trop. Med. and Hyg.*, 1914, 17, 305.
4. Castellani: *Jour. Trop. Med. and Hyg.*, 1920, 23, 101, 119, 133.
5. Fleisher and Wachowiak: *Am. Jour. Trop. Med.*, 1923, 3, 59.
6. Ashford: *AM. JOUR. MED. SCI.*, 1915, 150, 680.
7. Dold: *China Med. Jour.*, 1917, 31, 387; *Arch. f. Schiff's and Trop. Hyg.*, 1919, 23, 461.
8. Anderson: *Jour. Infect. Dis.*, 1917, 21, 341.

TWO CASES OF MYCOTIC ANEURYSM, GONOCOCCAL AND PNEUMOCOCCAL IN ORIGIN.

BY B. W. REIFENSTEIN, B.S., M.D.,

SYRACUSE, N. Y.

(From the Pathological Laboratory of the Peter Bent Brigham Hospital, Boston, Mass., and the Department of Pathology, Harvard Medical School.)

MYCOTIC aneurysms occur not infrequently during the course of an acute endocarditis or other acute infectious diseases. They form a distinct group, and, since relatively few are recognized during life, are of interest chiefly from the viewpoint of pathology.

The first description of an embolomycotic aneurysm apparently was made by Koch in 1851. His case was that of a ruptured mycotic aneurysm of the superior mesenteric artery which developed during an acute endocarditis. Since then the work of Ponfick, Eppinger and other investigators have placed this type of aneurysm on a definite etiological and pathological basis.

This type of aneurysm occurs for the most part in young adults, in marked contrast to the age period in which the luetic and arteriosclerotic aneurysms are found. It usually develops in connection with a concomitant acute endocarditis; occasionally, however, no primary endocarditis is present in the heart. The visceral and peripheral arteries in particular are sites of embolomycotic aneurysms; various portions of the aorta, however, may be involved by this definite pathological process. Many different bacteria such as streptococcus, staphylococcus, pneumococcus, the typhoid bacillus and even the gonococcus have given rise to this peculiar type of aneurysm.

The mechanism of formation of an aneurysm occurring in the smaller arteries is quite simple. This is due to an infected embolus plugging the artery usually at a point of bifurcation. The bacteria which gain entrance to the wall of the artery produce a mesaortitis with a resultant destruction of the elastic and muscular elements of the wall. Eventually the remaining parts of the media and adventitia bulge outward to form the sac of the aneurysm. However, not all cases observed, especially those developing in the aorta, follow this definite pathological sequence. Aneurysms occurring in the aorta are assumed to be due either to direct injury to the intima by bacteria or to the lodgment of an infected or bacterial embolus within the media. It is conceivable, that a congenital anomaly or an arteriosclerotic lesion may serve as a point of lessened resistance, and thus favor the direct lodgment of bacteria with resultant necrosis and aneurysm formation.

Many of the cases of mycotic aneurysms are associated with a latent symptomatology, so that their detection is not possible during life. Others, especially those occurring in the peripheral

arteries, give evidence of their presence by pain and swelling at the site of aneurysm. Occasionally the first indications of a mycotic aneurysm are the symptoms of internal hemorrhage due to rupture.

The 2 cases which comprise the subject of this article are of particular interest on account of the etiology and location of the aneurysms.

CASE I.—A female, housewife, aged twenty-nine years, with a history of a vaginal discharge of one and a half year's duration following a miscarriage, suffered for a period of two months prior to admission from dysuria, urgency, fever, chills, sweating, dyspnea and pain beneath the sternum. She had become progressively weaker and developed a tender spot on one toe.

Physical examination revealed emaciation, pallor, slight clubbing of fingers and subcutaneous petechiæ. The heart was slightly enlarged to the left and systolic thrills were present at the apex and at the pulmonic area. Systolic and diastolic murmurs were heard at the apex, and over the base a to-and-fro murmur was obtained. The blood-pressure was 128/54. The spleen was definitely palpable. The cervix was slightly reddened and contained a moderate amount of purulent discharge.

There was a moderate secondary anemia with a leukocytosis which ran as high as 31,950 at one examination. The urine showed albumin, red and white cells and casts at certain times. Four blood cultures were negative. The Wassermann reaction was negative. The gonococcus complement-fixation test was positive.

During the patient's seventy-one days in the hospital she ran a typical course of sepsis with various embolic phenomena. She developed a severe secondary anemia and became considerable emaciated before death.

Abstract of Necropsy. Anatomical Diagnosis: Mycotic aneurysms of ascending aorta (gonococcus); acute aortic endocarditis (gonococcus); organizing fibrinous pericarditis (gonococcus); hypertrophy and dilatation of the heart; bronchopneumonia; infarcts of spleen; ascites; chronic pleuritis.

General examination of the body showed petechiæ and several decubiti. The peritoneal cavity contained 1400 cc of serous fluid. Fibrous adhesions were present between the spleen and diaphragm. The pleural cavities contained old fibrous adhesions.

The peritoneal cavity contained 200 cc of a serofibrinous fluid. The pericardium was covered with a thick exudate of yellowish fibrin which was thrown up into ridges producing a shaggy appearance. In several places the exudate was reddish in color, tough and adherent, due to organization.

The heart was enlarged, weighing about 450 gm. The aortic valve was slightly thickened and contained soft, granular, pinkish vegetations 3 to 4 mm. in diameter. The arch of the aorta was dilated. Immediately above the aortic valve were several small



FIG. 1.—Case I. Mycotic aneurysm (gonococcus). Note also the fibrinous exudate on the pericardium.

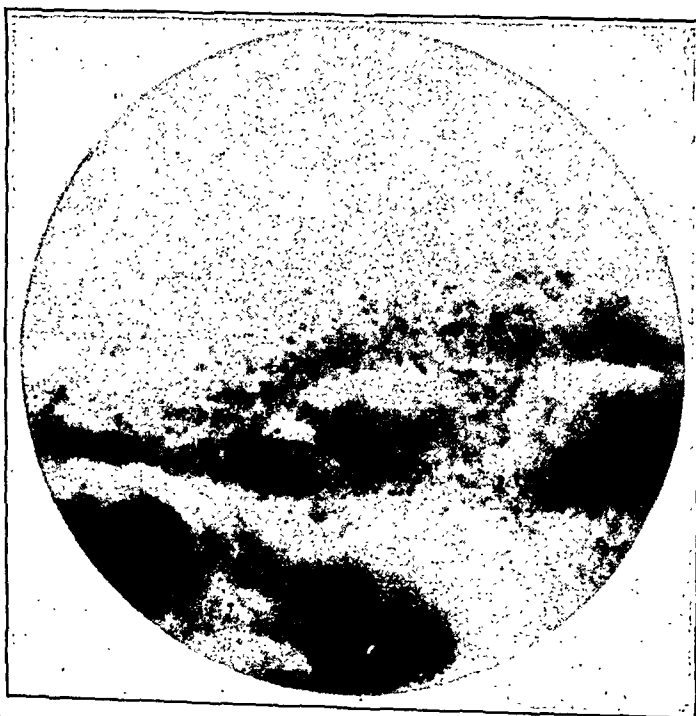


FIG. 2.—Case I. Mycotic aneurysm (gonococcus). High power of vegetations showing clumps of biscuit-shaped organisms.

aneurysms 0.5 to 1 cm. in diameter. They were sharply outlined, bulged out from the right side of the aorta and were filled with granular thrombi. On the posterior aspect of the ascending aorta near the arch was another large aneurysm extending inferiorly and to the right beneath the bifurcation of the trachea for a distance of 4.5 cm. It measured 2.5 cm. in diameter, was sharply outlined and filled with granular thrombi. At one point on the orifice of this sac, a small dissecting aneurysm took origin and extended along the ascending aorta for a distance of 1.5 cm. The remainder of the heart and aorta was negative.

The lungs showed patches of bronchopneumonia. There was no communication between the large aneurysm and the right lung. The spleen was slightly enlarged and contained several small infarcts. The kidneys were somewhat pale and not unusual on section. The uterus and adnexa showed no signs of any inflammatory process.

Smears from the exudate on the pericardium, the vegetations on the aortic valve, and from the thrombi in the aneurysms revealed many Gram-negative diplococci in colony formation. Many of the Gram-negative biscuit-shaped organisms were intracellular. Special starch agar media failed to grow the gonococcus from the blood and vegetations. Cultures on ordinary media showed several contaminating organisms.

Microscopical sections of the vegetations stained with Giemsa disclosed many colonies of bacteria and scattered isolated bacteria occurring as flattened diplococci. Many bacteria were incorporated in polymorphonuclear leukocytes. Sections of the spleen showed infarction. Kidney sections revealed small thrombi in the glomeruli with partial hyalinization. Sections of the uterus were negative.

CASE II.—A school boy, aged ten and a half years, suffered from increasing cough and fever. At approximately the age of two, the patient had developed a mild endocarditis, which in subsequent years did not incapacitate him. The present illness began four weeks before death with an attack of a then prevailing epidemic of nasopharyngitis. At no time was he very ill, and the chief symptoms were cough and fever. Increasing frequency of cough resulted in a consultation at which nothing abnormal could be found in the chest. A few days before death the patient had respiratory distress. While in apparently good condition, he had a sudden hemorrhage from the mouth and died immediately.

Abstract of Autopsy. The autopsy was performed in a private home after the body had been embalmed.

Anatomical Diagnosis: Mycotic aneurysm (pneumococcus) of descending aorta with rupture into esophagus and lung; slight mitral endocarditis (chronic); congenital anomaly of thoracic aorta; slight hypertrophy of the heart; acute splenitis.

In the left pleural cavity, the medial surfaces of both lobes of the



FIG. 3.—Case II. Mycotic aneurysm (pneumococcus). Aneurysm filled with thrombus in descending aorta.

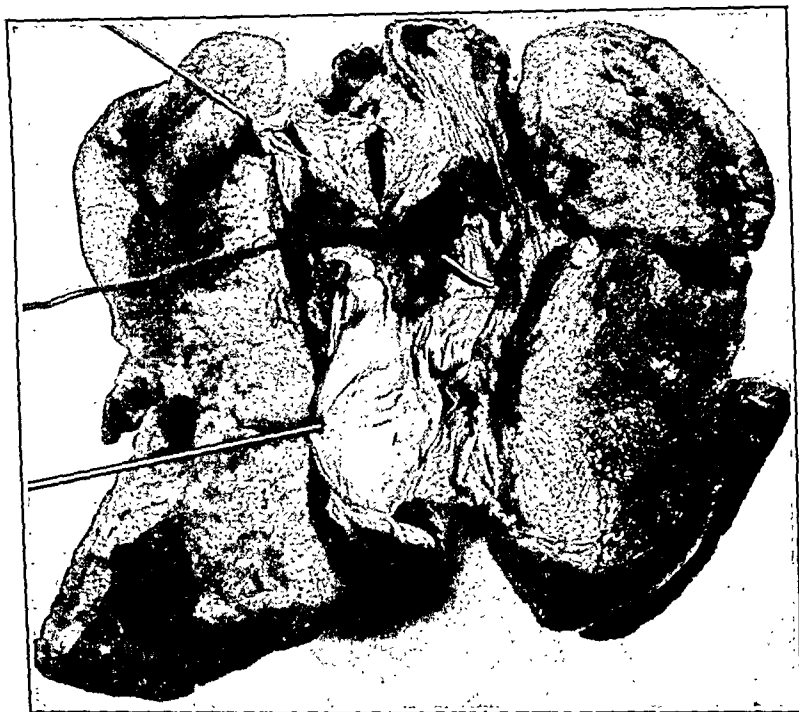


FIG. 4.—Case II. Mycotic aneurysm (pneumococcus). Aorta pulled over to the right so as to show the rupture into the esophagus.

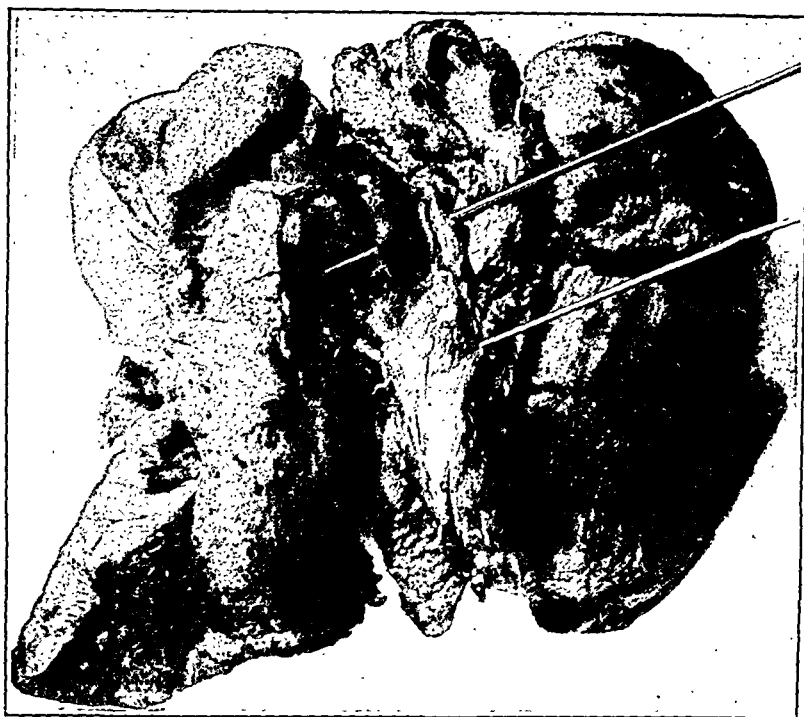


FIG. 5.—Case II. Mycotic aneurysm (pneumococcus). Aorta and esophagus drawn over to the right so as to reveal the dissection in prevertebral space and adhesions to left lung.

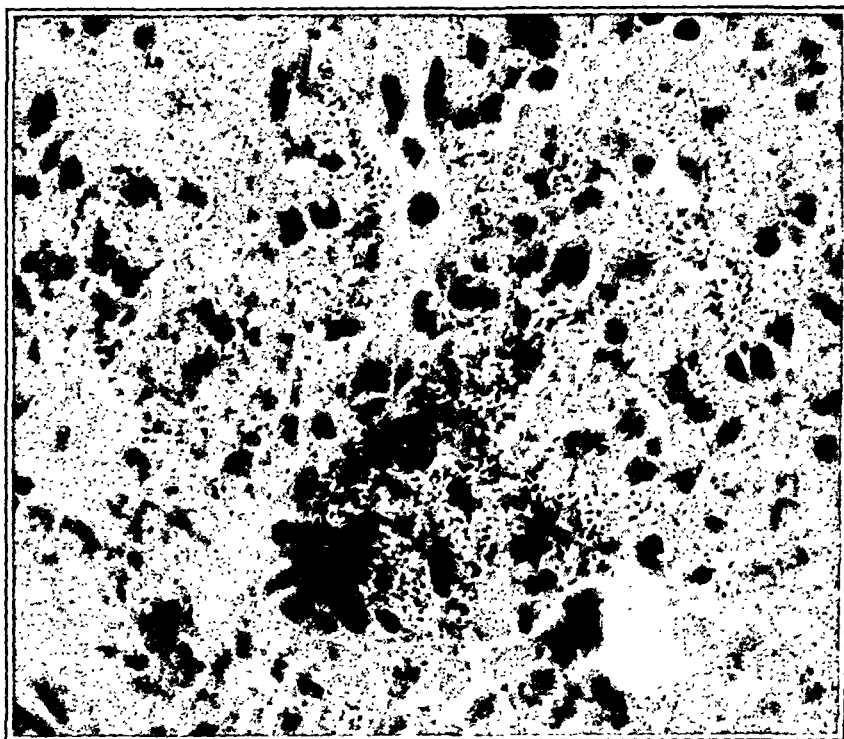


FIG. 6.—Case II. Mycotic aneurysm (pneumococcus). High power of wall of aorta showing lanceolate diplococci and inflammatory reaction.

lung were tightly adherent to a swelling over the vertebræ. Separation of the adhesions revealed a cavity 5 cm. in diameter, filled with a peculiar friable clot. The adjacent lung tissue was somewhat firm.

The heart was hypertrophied. There was a rather pronounced thickening of the junction of the anterior and posterior segments on the right side of the mitral valve. The ascending aorta, up to the origin of the innominate artery, was slightly dilated, measuring 4 cm. in circumference. A marked constriction of the aorta formed by a yellowish ridge, was found 2.5 cm. below the origin of the left subclavian artery. Above the constriction, there was slight thinning and bulging of the aortic wall with some barely visible transverse striations. Below the constriction was a marked dilation with a hole involving the anterior and left wall of the aorta. The irregularly outlined orifice extended downward for 3.5 cm. and involved at least five-sixths of the circumference of the aorta. At one point a sharp break in the wall of the aorta opened into a cavity filled with gray crumbly clot. This cavity was walled off by vertebræ and lung tissue. The esophagus was markedly deviated to the right and contained a cavity on the left side measuring 5.5 cm. vertically and 3 cm. laterally. This cavity communicated with the aortic blood stream by means of numerous ragged openings through the aneurysmal wall. The left primary bronchus was pressed downward and forward, but showed no absorption of cartilage.

The lungs showed small red areas due to insufflation of blood. The spleen was enlarged, soft, almost diffuent. The remaining organs were negative.

Sections through the aortic wall at the orifice of the aneurysm disclosed marked necrosis extending from the edge into the wall of the aorta. For a considerable distance the aorta could be recognized only by the remaining elastic laminae, while the smooth muscle was replaced by necrotic tissue and the polymorphonuclear leukocytes. Giemsa stained sections showed many diplococci both intracellular and extracellular, which could not be demonstrated by Gram's stain. The striking thing in the aortic wall at the edge of the aneurysm was the definite abscess formation in addition to the diffuse infiltration of polymorphonuclear leukocytes.

Discussion. The first case is evidently one on gonococcus septicemia. The history of vaginal discharge previous to the onset of illness, the absence of a history of rheumatism, the presence of signs of valvular disease most marked over the aortic valve, the inability to obtain a positive blood culture and the positive gonococcus complement-fixation test established this diagnosis during life. The identification of an organism possessing the tinctorial and morphological characteristics of the gonococcus at autopsy further substantiated the diagnosis of gonococcus septicemia even though there were no localizing lesions found in the genital tract.

Thayer,³ in a recent review of gonorrheal endocarditis found that the gonococcus usually involves healthy, previous unaffected valves; that the aortic valve is most commonly involved; that grave constitutional symptoms are present; and that gonorrheal endocarditis is a malignant process, pursuing a progressive and fatal course usually within five to nine weeks. The writer's case, though of longer duration, fifteen to eighteen weeks, possessed all the other characteristics of gonorrheal endocarditis. In this case the pericarditis, also due to the gonococcus, arose by direct extension of the infection through the wall of the largest aneurysm into the pericardial sac.

The second case illustrates what an extensive process there may be in the aorta with relatively few or no symptoms, except those due to pressure. The process was acute, extending over a period of only four weeks. The mycotic aneurysm developed without any associated acute endocarditis and no doubt was due to direct injury of the intima by the pneumococcus, at the site of the slight, presumably congenital, constriction noted below the arch.

Conclusions. 1. The etiological factor has been determined with fair accuracy in two cases of mycotic aneurysms.

2. One case due to the gonococcus was insidious in onset, protracted in duration and presented all the classical signs and symptoms of a septicemia; the other due to the pneumococcus was of an acute nature and gave but relatively few localizing signs.

3. The possibility of the formation and rupture of mycotic aneurysms should be borne in mind in all cases of acute infectious diseases.

REFERENCES.

1. Libman, E.: *Proc. New York Path. Soc.*, 1905-1906, 5, 43, 88.
2. Lewis and Schrager: *Jour. Am. Med. Assn.*, 1909, 53, 1808.
3. Thayer, W. S.: *Johns Hopkins Hosp. Bull.*, 1922, 33, 361.

THE HUMAN DYING HEART.

BY MORRIS H. KAHN, M.A., M.D.,

AND

ISRAEL GOLDSTEIN, A.B., B.S., M.D.,

NEW YORK.

(From the Department of Cardiovascular Diseases, Beth Israel Hospital, New York City.)

Introduction. In the physical processes of individual organs, death is a more or less relative phenomenon. This applies with especial emphasis to the heart.

There are various stages in its progressive functional and structural deterioration. In the early stages, as the probable result of nervous influences, there may be a cessation of function which under stimulation can return to normal. What may appear clinically as absolute death may in reality be only a depression of outward manifestations. Second, because of chemical changes in the blood or in the tissues, the capacity to function may be so far depressed that its recovery under stimulation is unlikely. The final stage, from which no recovery is possible, is the dissolution or absolute death of the tissue both in chemical reaction and in microscopical appearance. It is during these stages that the fascinating borderline phenomena between life and death take place.

The controlling factors of the heart's action may be divided into:

1. The central regulating and controlling mechanism in the medulla.
2. The autonomic function situated in the heart as specialized nodal tissue.
3. The heart muscle itself and its blood supply.

It is probable that all these factors are terminally attacked in varying proportions, the degree depending upon their vulnerability.

It may be assumed theoretically that in the derangement of the nervous control of the cardiac mechanism the first disturbances would affect the main controlling centers. With depression of these the subsidiary centers would then become dominant.

One of the important changes that takes place in the dying individual is inadequate tissue oxidation with an accumulation of carbon dioxide. The premonitory manifestations in the dying heart are partly the result of this chemical change. The vagus centers in the medulla are stimulated, producing inhibition of the most susceptible heart regions; that is, the atrial node and the conducting tissue in the heart are depressed. Because of the oxygen deficiency, the muscle tissue may also evince peculiarities of action.

The Mechanism of the Dying Heart. The phenomena of death as they are revealed by the electrocardiogram relate to the disturbances of function immediately preceding the absolute cessation of all heart activity.

It was formerly a point of considerable interest as to what portion of the heart is the *ultimum moriens*. It was found in a number of studies of animals during asphyxia that the most viable parts of the heart are located in the right auricle.¹ At times, in the dying heart, the auricular appendage showed the strongest hold on life and was the last part to retain the power of contraction. Others had found that the region about the mouth of the vena cava manifested contractions after all other regions of the heart became quiescent,² and

¹ Eyster and Meek: *Heart*, 1913-1914, 5, 137.

² MacWilliams: *Jour. Physiol.*, 1888, 9, 167.

still others found it at various regions between the atrial node and the auriculoventricular node.³

It may be that in the dying asphyxiated heart the impulse arises in a region different from that in which it arose in the same heart beating under normal conditions. It must be remembered also that the properties of the heart muscle are present in varying degrees relative to each other in different parts of the heart.⁴ Thus certain regions may show no visible contractions, although automaticity or excitation may arise from them. That is, cessation of all functions does not take place at the same time.

It has been shown that after complete auriculoventricular dissociation from asphyxia (in the cat) the auricular contractions almost always abruptly disappear.⁵ This is due to the abrupt termination of the function of the sino-auricular node, the auriculoventricular node continuing to control the ventricle. When this happens the heart will not recover although re-oxygenated. This change would account fully for the end curves in simple asphyxia and in certain of the curves of the dying human heart.

The beats of the dying heart are slowly conducted, and the contraction waves may often be seen to originate near the mouths of the great veins and to be conducted from them.⁶

In a very extensive experimental study on dogs and rabbits by Yamada, death of the heart was induced by a great variety of mechanical causes, by the action of chemicals, by drugs and by anaphylaxis.⁷ In these experiments the general sequence of events corresponded to those found in asphyxia.

There was first a slowing of the heart action with early failure of the atrial node which was often temporary and caused by vagus stimulation. This was followed by dissociation between the auricles and ventricles. The auricular contractions stopped more abruptly than the ventricular. The nodal control of the ventricles lasted a varying length of time, during which period the rate of the auricles and ventricles slowed. There was usually a recovery of sinus control of the heart, again followed by complete dissociation. Either the auricles or the ventricles persisted longer. In the pre-terminal stage, there were variations in the form of the auricular and ventricular waves with characteristic and striking changes. There also occurred attacks of auricular or ventricular tachysystole. Some of these have their analogue in the dying human heart.

That the main changes were due to vagus control was shown in a parallel series of experiments after vagus section. In these sinus arrhythmia disappeared before asphyxiation and the tachycardia

³ Hirschfelder and Eyster: *Am. Jour. Physiol.*, 1907, 18, 221.

⁴ Hoffmann: *Arch. f. d. ges. Physiol.*, 1910, 133, 552.

⁵ Lewis, White and Meakins: *Heart*, 1913-1914, 5, 289.

⁶ Lewis: *Mechanism and Graphic Registration of the Heart-beat*, 1921, Chap. V, p. 70.

⁷ Yamada: *Mitt. a. d. med. Fakult., Univ. Tokyo*, 1920, 25, 97.

persisted for a long time. The early bradycardia and complete or incomplete heart-block in unvagotomized animals were thus shown to be due to central vagus stimulation. The abrupt cessation of the auricular contractions, more sudden than the ventricular, is explained by the greater sensitiveness of the atrial node than the auriculoventricular node to vagus stimulation. The periods of ventricular tachysystole that occurred were explained by cessation of the inhibitory action of the vagi and possibly also by stimulation of the accelerators. The impulse formation first migrated to the auriculoventricular node and then to some tertiary ventricular center. The latter produced abnormal ventricular complexes. The auricular contractions continued for a period after the ventricles had ceased beating.

Some of the vagus effects may be due to peripheral irritation of its endings in the lungs, reflexly causing complete heart-block. The occurrence of ventricular extrasystoles may be the result of extracardial vagus effects. In cases of embolism in the coronary artery, they may be due to the direct presence of air in the heart, reflexly affecting the vagi.

It seems probable that these changes in the rate and in the form of the complexes are dependent on changes in vagus tone. Diminution of the size of *P* and *T* waves occurring with periods of slow rate resemble the electrical complexes seen when the vagus tone is raised.⁸

It has been shown that part of any of the cardiac centers will induce the same rhythm as the entire center.⁹ This is especially true for the veins and sinus and less for the auriculoventricular node and the bulbus. This also supports the view that vagus influences induce the early changes in the mechanism of the dying heart. Since the vagus would influence the nodal regions in its entirety more likely than would a change in the circulatory supply, the abrupt cessation of sinus rhythm also suggests a vagus effect.

The termination of attacks of ventricular fibrillation in death has been repeatedly observed.¹⁰ The heart rarely recovers its normal mechanism.¹¹

The Human Dying Heart. The first electrocardiographic study of the human dying heart was presented very briefly before a medical society in Germany in 1911.¹² In three fatal cases of diphtheria, there were found variable and abnormal *QRS* complexes. In 1 case, at least, there was complete auriculoventricular dissociation.

Seven patients dying from acute infectious diseases without cardiac involvement were studied by means of the electrocardiograph

⁸ Rothberger and Winterberg: *Arch. f. d. ges. Physiol.*, 1910, 135, 506.

⁹ v. Skramlik: *Arch. f. Physiol.*, 1920, 183, 109.

¹⁰ Levy: *Brit. Med. Jour.*, 1914, 2, 502.

¹¹ Robinson and Bredeck: *Arch. Int. Med.*, 1917, 20, 725.

¹² Rohmer: *München. med. Wehnschr.*, 1911, 58, 2358.

in 1912.¹³ In 4 of these, the ventricle outlasted the auricle and in 2 the opposite occurred. In 1 case, both stopped at apparently the same time. Arrhythmias occurred with delay in conduction time in 5 cases and other arrhythmias such as heart-block, ventricular extrasystoles, tachycardia and ventricular fibrillation took place without characteristic sequence.

"Characteristic changes in the ventricular complex of the electrocardiograms occurred in all the records. They consisted of a decrease in the size of the *R* wave and an increase in the size of the *T* wave, and a tendency to a fusion of these waves. There was usually but little change in the duration of the ventricular complexes as the cardiac activity gradually ceased. The change in the form of the ventricular electrical complexes indicates that the course of the stimulus and the manner of the contraction of the muscle were abnormal. The fact that the *R* wave became gradually prolonged suggests that the conduction of the stimulus through the ventricular walls became delayed as the heart died. The fact that after death there is a continuation of cardiac muscular activity sufficient to cause a difference in electrical potential between the two sides of the body does not necessarily mean that a ventricular systole in the sense of muscular shortening takes place. It has been observed experimentally that well defined electrical complexes may be caused by cardiac activity which cannot be seen or recorded graphically. As the duration of the ventricular complexes characteristic of the dying heart usually does not differ markedly from the duration of the complexes before clinical death, it seems probable that the entire musculature of the ventricles participates in the contraction; as definite shortening, or at least a marked change in duration, would be expected if only a part of the ventricular musculature participated in the activity which produced the complex."

Three other cases with terminal records of dying hearts were reported.¹⁴ All were cases of cardiac failure with myocarditis. In these, clinically, there was marked impairment of the respiratory function with rapidly increasing insufficiency of oxygen and accumulation of carbon dioxide. There was slowing of the heart-rate with manifest auriculoventricular nodal control. There were periods of auricular and ventricular fibrillation and paroxysmal tachycardia of various types. There was usually a decrease in the amplitude of the main waves and widening of the *QRS* wave; the *T* wave became negative in 1 of the cases.

In an experimental study on the effects of low oxygen tension on the heart mechanism it was found that until a certain critical stage in the anoxemia is reached, the general changes in the electrocardiogram are slight.¹⁵ These consist of shortened *P-R* interval

¹³ Robinson: Jour. Exper. Med., 1912, 16, 291.

¹⁴ Dieuaide and Davidson: Arch. Int. Med., 1921, 28, 663.

¹⁵ Greene: Arch. Int. Med., 1921, 27, 517; Am. Jour. Physiol., 1922, 60, 155.

(increased conduction rate), coincident with increased heart-rate, decrease in total time of the R - T interval, decreased amplitude of the T wave with maximum retardation toward the terminal phase, and sometimes a diphasic or negative T wave.

With extreme oxygen want, there occur great slowing of rate; progressive descending displacement of the pacemaker, or center of rhythm production, toward and into the auriculoventricular node; and interference with normal conduction leading to dissociation. Later, conduction is suppressed with maintenance of auricular beats. There is also suppression of cardiac function in the descending direction, both as to rhythm production and conduction.

The changes that take place in the auricular complex may be very varied and, for the convenience of description, may be said to present the following types: Normal, inverted, diphasic, sudden rise with gradual fall, notched, double, auricular flutter and auricular fibrillation.

These may be combined with deformities of the ventricular excitation wave, which also for the convenience of description may be designated as follows: Normal, notching and widening of R , lower amplitude of R , union of R and T , inversion of T , absence of T , diphasic ventricular wave, ventricular flutter, ventricular fibrillation and abortive ventricular fibrillation.

We purpose in this communication to report the study of the dying human heart in 7 cases. In these, records were obtained for some time previous to and during the various stages of death. In all we obtained all or some of the last electrical complexes which followed the period of clinical death.

History Report. CASE I.—L. S., aged thirty-six years, was observed as a case of lobar pneumonia.

Important in the history of this patient was the persistent nasal obstruction for two years. During this time he suffered from frontal headaches of increasing frequency and severity. For three months before he died they were continuous. There was no precordial pain, dyspnea or palpitation.

Physical examination revealed almost complete nasal obstruction to breathing and total deafness of the right ear and less of the left ear. The heart was enlarged; its sounds were fair. The blood pressure was 100/60 mm.

The urine was negative. The blood Wassermann test was negative and the blood chemistry was negative. The blood showed about 6000 leukocytes, 60 per cent polymorphonuclears and 40 per cent large mononuclears. Roentgen-ray showed clouding of the antra. The temperature was normal.

Course: Following a nasal operation for turbinate-septal adhesions, the temperature rose to 104° F. and remained high to the end. The patient's condition became poor the day before he died. There

was cyanosis and bronchial breathing over the lower pulmonary lobes posteriorly. He died with cardiac failure.

Diagnosis: Bilateral lobar pneumonia.

Electrocardiographic Studies. Some hours before the patient died, the heart showed tachycardia, a rate of 125 per minute, slight left ventricular preponderance and *P* wave finely notched in leads I and II. (Fig. 1a).

The terminal records were taken in Lead II. Respiration stopped about two minutes before the audible heart beats. Shortly before clinical death there was distinct evidence of sinus arrhythmia. This was not as marked throughout the record but occurred rather spasmodically.

A few minutes before death, however, there was slowing of the sinus rate with marked sinus arrhythmia. At one point about seven minutes before the end of the record, the auricular contraction seemed to occur doubled (*b*). A minute later there was no evidence of sinus function and the *P* wave was suddenly lost from the electrocardiogram. The ventricular wave showed no change (*c*). The failure of the sinus to act was promptly replaced by nodal rhythm after a delay of 0.07 second.

The nodal rate increased slightly and progressively. At the same time, the *QRS* wave widened gradually and became slightly notched (*d*). In occasional cycles its course through the ventricles was aberrant. The origin of some of these beats was in the region of the auriculoventricular node, showing an irritability of the junctional tissue. Preceding two of these nodal cycles, a diphasic *P* wave occurred, with shortening of the *P-R* interval. (These are not reproduced in the figure.) Soon after this, there was a resumption of sinus rhythm with no delay in conduction. The *P* wave, however, was somewhat changed in contour; it was small with an abrupt elevation and a gradual fall (*d*).

The sinus rate continued slightly faster than the preceding nodal rate, without arrhythmia. The *QRS* complex had meanwhile become considerably widened with very much notching and thickening of the ascending limb (*e*).

Conduction, during all this time, was rather quick, the *P-R* interval being about 0.08 second. Suddenly, the sinus failed and the auricular beats were again lost. The nodal beats were slower except for irregular paroxysms, as in the first part of strip *f*. When the sinus did recover, it found a partial block, the *P-R* interval being prolonged to 0.48 second (*g*).

The auricular and ventricular rates were about the same, 67 beats a minute. The auricle, however, progressively slowed with slight variation in conduction defect and at times failure of the sinus.

The main deflections of the *QRS* wave diminished in amplitude or voltage and became more and more continuous with *T*. The

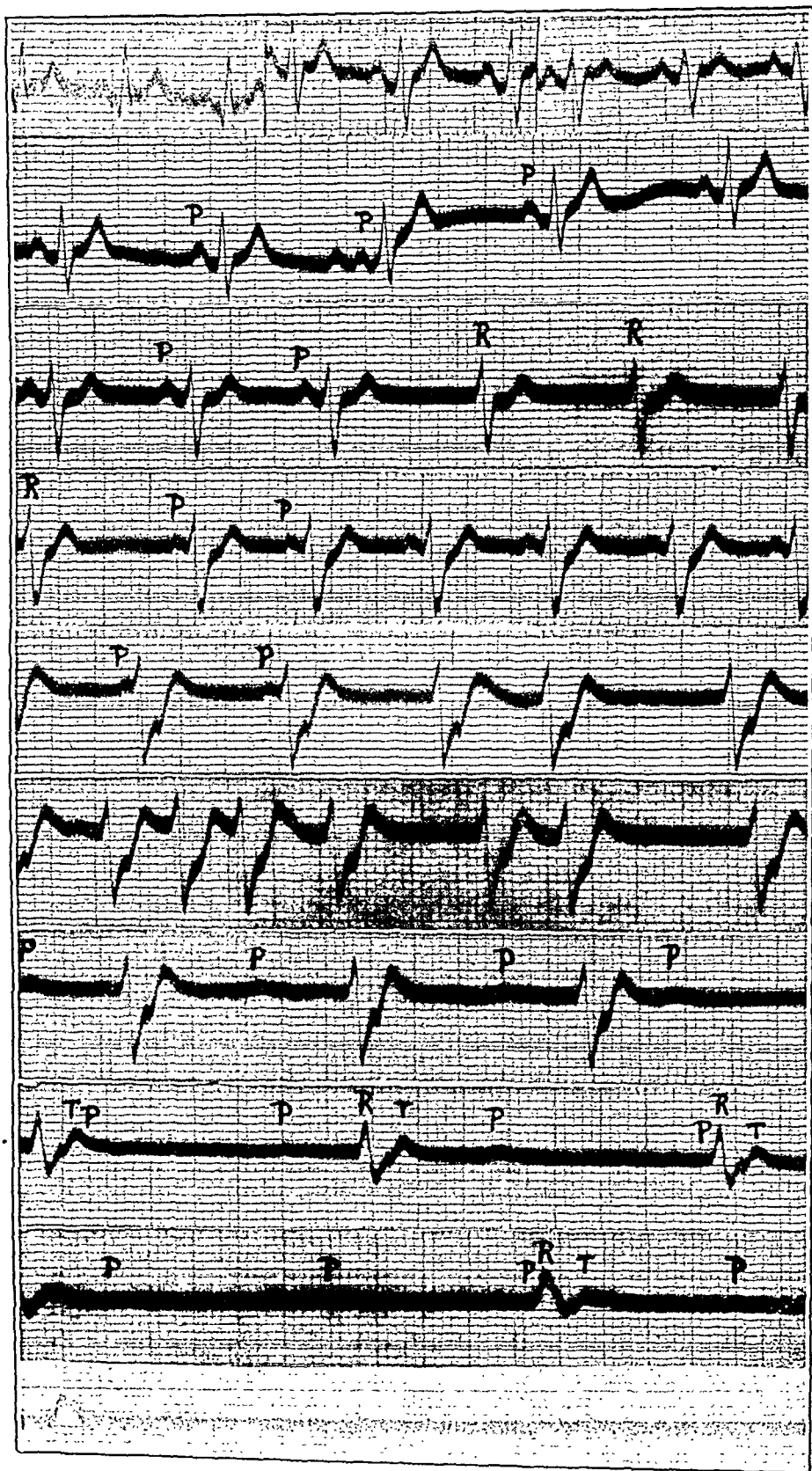


FIG. 1.*—Sequence of prints of the dying heart in Case I, analyzed in the text.

* In all photographs, (except Fig. 4): Abscissæ 1 division = 0.04 second. Ordinates 1 division = 10^{-4} volts. The strips are designated alphabetically from above down.

sinus rate continued at 67 and the ventricular rate at 25 per minute with complete auriculoventricular dissociation (*h-i*).

The intervals between the last few ventricular cycles were 5 to 7 seconds. Sinus activity was evidenced by *P* waves at a rate of about 65 per minute for a period of about thirty seconds after the last cycle (*j*).

Summary and Discussion of Case I. Thus we have in this case, the following sequence of events: (1) Sinus arrhythmia, depression and failure; (2) nodal rhythm with its irritability; (3) bundle-branch conduction failure or intraventricular conduction defect; (4) intermittent recovery and exhaustion of the sinus; (5) progressive nodal exhaustion with changes in the *QRS* and *T* waves; (6) terminal sinus rhythmic impulses for a long period after the last nodal cycle.

It is with some doubt that the wave in strip "b" is spoken of as a double auricular wave. There are several reasons why this interpretation can be given. Although not exactly a reproduction, its contour resembles the other waves in several ways. Its duration is the same, its height, angles of rise and fall are the same, and especially pertinent is its notching which very much resembles the other *P* waves.

It is very interesting to note that it occurs at the end of expiration. Inspiration is apparently indicated in the very fine fibrillatory waves during the next cycle. This may have been the patient's last gasp for breath, and with this there is a general elevation of the entire isoelectric level. What is difficult to explain is the occurrence of normal conduction during the refractory period following the abnormal wave. But, when the vagi are stimulated, the absolute refractory period of the muscle is greatly reduced.¹⁶ It is also hard to see why the ventricular cycle did not immediately follow the first *P* wave. One must postulate a momentary blocking of the premature stimulus. It is thus a matter of conjecture as to the exact interpretation, yet we are loathe to dismiss it as an artefact.

The remainder of the record is almost self-explanatory and requires no further discussion.

CASE II.—S. K., aged forty-nine years, was observed as a case of cardiorenal disease.

About four months before death, after a heavy meal, the patient slept a short time and suddenly awoke unable to breathe. During that night he had several such attacks with a fearful sensation as if the chest were pressed in a vice. The following morning he had some hemoptysis. One week later, a severe attack occurred with a sense of impending death which was relieved by heat applied to his chest. He had many similar attacks, the worst occurring about three weeks before death.

¹⁶ Lewis, Drury and Iliescu: *Heart*, 1921, 8, 311.

Physical examination showed slight cyanosis and dyspnea. There were a few rales posteriorly at the bases of both lungs. The heart was enlarged both to the left and right. Over the entire precordium, but heard loudest at the aortic area, there was a systolic and diastolic murmur. Over the mitral area the systolic murmur was rough, but not transmitted. Corrigan and capillary pulses and a pistol-shot sound in the brachials were present. The liver and spleen were just palpable below the costal margin. There was slight edema of the extremities and clubbing of the fingers.

The urine showed a moderate amount of albumin and hyalin and granular casts. The phenolsulphonaphthalein test showed 20 per cent in two hours. The blood count showed 12,400 leukocytes and 70 per cent polymorphonuclears. The blood Wassermann test was weakly positive, but the spinal fluid was negative. Roentgen-ray examination showed marked enlargement of the heart to the right and left. There was also pneumonic infiltration and some fluid on the right side. The temperature was about 100° F. throughout. Blood cultures were negative. The blood-pressure was about 150/66 mm. The pulse-rate was about 100. Respirations were about 30 per minute at first and about 40 toward the end.

Course: Three days before death, the patient became more stuporous and irrational with marked respiratory distress.

Diagnosis: Chronic cardiovalvular disease and chronic parenchymatous nephritis.

Autopsy findings showed chronic congestion of the lungs. The heart was very much hypertrophied and the left ventricle was greatly dilated. The muscle was firm and smooth. The edges of the aortic valves were very thick and the seat of numerous large white nodular firm vegetations. The bases of the valves were thin and free from thickening. The mitral valve was normal. The auricles were dilated; the inner walls were smooth. The aorta was free. There was no sclerosis. The liver was enlarged and showed an advanced nutmeg change. The spleen also was enlarged and there was chronic congestion of the kidneys.

Anatomical Diagnosis: Acute vegetative endocarditis, (no bacteria), chronic congestion of the lungs, liver, spleen and kidneys.

Electrocardiographic Studies (Fig. 2). Several days before death the electrocardiogram showed a slight diphasic curving of the *T* wave in Lead III. The ascending arm of *QRS* was thickened in Lead I and finely notched in Lead III. Just before the patient died, the first evidence in the electrocardiogram was failure of the sinus and of auricular activity and a complete assumption of control by the auriculoventricular node (*b*). Besides, it must be noted that there was variation in the height of *R* with irregularity in its rhythm (*c*). This continued with progressive but irregular slowing of the nodal rhythm. The *T* wave was inverted, and at times there were fibrillatory waves suggesting auricular action. The *T* wave

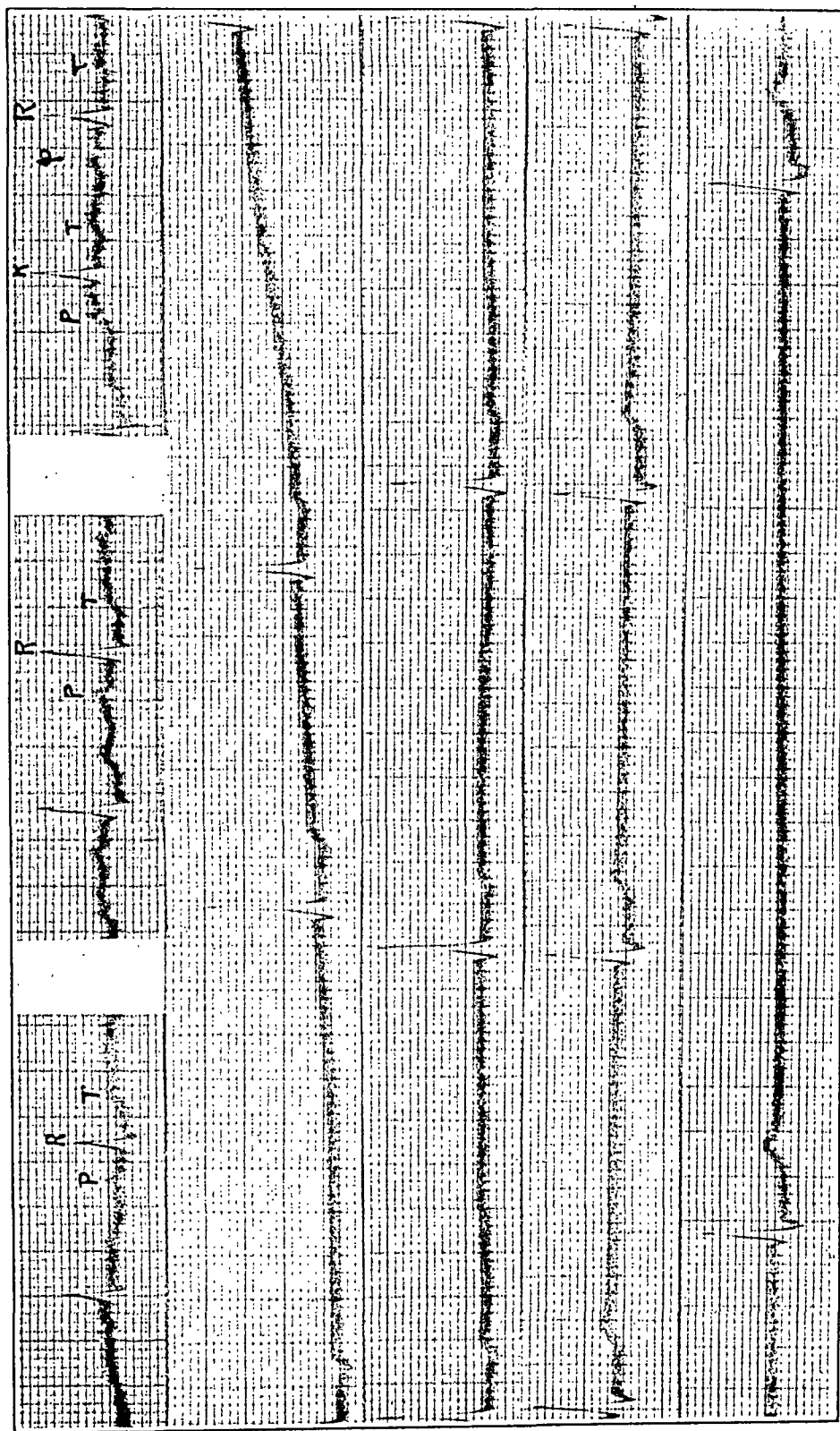


FIG. 2.—Sequence of prints of the dying heart in Case II, analyzed in the text.

gradually showed less inversion and more of an upright phase and finally became entirely upright (*d*). The *S-T* phase became slightly prolonged. After a very marked slowing, the last three or four ventricular beats showed distinct alteration in the contour of *S* (*e*). The interval between the last and penultimate beats was about ten seconds. About thirty seconds after the last beat, several peculiar movements of the string occurred, evidencing final ventricular contraction of extraordinary form.

Summary and Discussion of Case II. The sequence of events in this case may be summarized as follows: (1) Early failure of the atrial node without recovery; (2) nodal control with irregular rhythm; (3) progressive nodal slowing; (4) prolongation of the *S-T* phase; (5) change in direction of the *T* wave.

That pulsus alternans bears a close relation to the force developed by the ventricular contraction is well known. That is why it is of great clinical significance. This alternation of energy of the ventricular contractions produces a pulse in which the alternate beats are of lower amplitude. The electrocardiogram may indicate this alternation as well as the pulse-wave. (Fig. 2*c*).

Pulsus alternans also bears a direct relation to the changes in pressure in the left ventricle and in the arterial circulation. The amplitude of the pulse-wave is determined essentially by the capacity of contraction of the heart, that is, by the quantity of blood driven out into the aorta by the left ventricle during systole. This quantity depends upon the amount of filling of the left ventricle before systole, the pressure in the ventricle, and third the pressure in the aorta.

Pulsus alternans is therefore to be explained in many instances by the fact that the force of the ventricle can overcome a certain amount of aortic pressure. When, after a complete contraction, the aortic pressure rises, the energy of the next heart beat is partly utilized in overcoming some of this pressure before a pulse-wave becomes apparent. It is likely that both factors, the energy of systole which is primary in the muscle and the influence of arterial pressure, are the causes of alternation in a feeble heart muscle.¹⁷ Vagus stimulation may abolish alternation by reducing the rate of the heart.¹⁸

CASE III.—B. K., aged fifty-four years, was observed as a case of cardiorenal disease.

The patient had suffered from frequent attacks of tonsillitis. He had had a chancre at the age of twenty-one and scotomata and headaches for years. His last illness began rapidly seven months before death with swelling of the face and extremities and ascites. He had dyspnea and frequent vomiting.

¹⁷ Dasbach: Onderzoekingen Physiol. Lab. Einthoven, Leiden, 1922, p. 118.

¹⁸ Rihl: Ztschr. f. exper. Path. u. Therap., 1912, 10, 8.

Physical examination showed pasty pallor, dyspnea, ascites and anasarca. His chest was emphysematous. The heart apex-beat was not visible and its sounds were weak and distant. The extremities were extremely edematous. The blood-pressure was 130/105 mm.

The urine showed a large amount of albumin and many hyalin and granular casts. The blood showed a slight secondary anemia. The blood Wassermann test was negative. The temperature on admission was normal.

Course: The abdomen was tapped of 2500 cc of colorless fluid, the examination of which showed: Cytology 10 cells per c.mm., 10 per cent polymorphonuclears and 90 per cent lymphocytes. After the tapping, the patient had a chill and the temperature rose to 103° F. The pulse became weak and irregular. He died with pulmonary edema several days after.

Diagnosis: Chronic cardionephritis.

Electrocardiographic Studies (Fig. 3). Before the patient died, the heart-rate was 90 per minute and gradually with slight variation in its slowing, it fell to 50 beats per minute. The *P* wave was very slight. The *QRS* wave was minute in Lead III, consisting of a diphasic wave directed chiefly downward and then upward, 1 mm. above and 1 mm. below the abscissa level. The *T* wave became inverted in Lead II after the rate slowed.

The last record was taken in Lead II after the patient was clinically dead. No heart sounds were audible and the peripheral circulation had apparently stopped. The record begins with a normal *P-R-T* sequence and a rate of 60 per minute. There is distinct sinus arrhythmia with slowing at times to the rate of 50 per minute. *P* is upright and slight. The *P-R* interval is at first 0.22 second and gradually increases to 0.4 second toward the end of this strip of record.

The ventricular complex changes as the heart failure progresses. It is upright and slight and the descending arm thickens as it descends. With the progress of failure, *S* terminates more and more above the isoelectric level and continues horizontally into an inverted *T*. The *T* wave tends to become inverted at first and later progressively isoelectric. One early ventricular extrasystole is noted arising from the base of the heart. (No. 103-2).

The record was continued in Lead II, but the amplitude of the string was doubled. (No. 104). The auriculoventricular node has assumed control. There is complete dissociation between the auricles and ventricles. The auricular rate is about 45 per minute while the ventricular is about 38. The *QRS* wave has become extremely widened. After the first few cycles *T* is no longer to be seen. There is progressive sinus slowing and marked nodal slowing. Momentary ventricular fibrillation occurs with temporary recovery. (No. 104-11). The last ventricular beat is followed by auricular

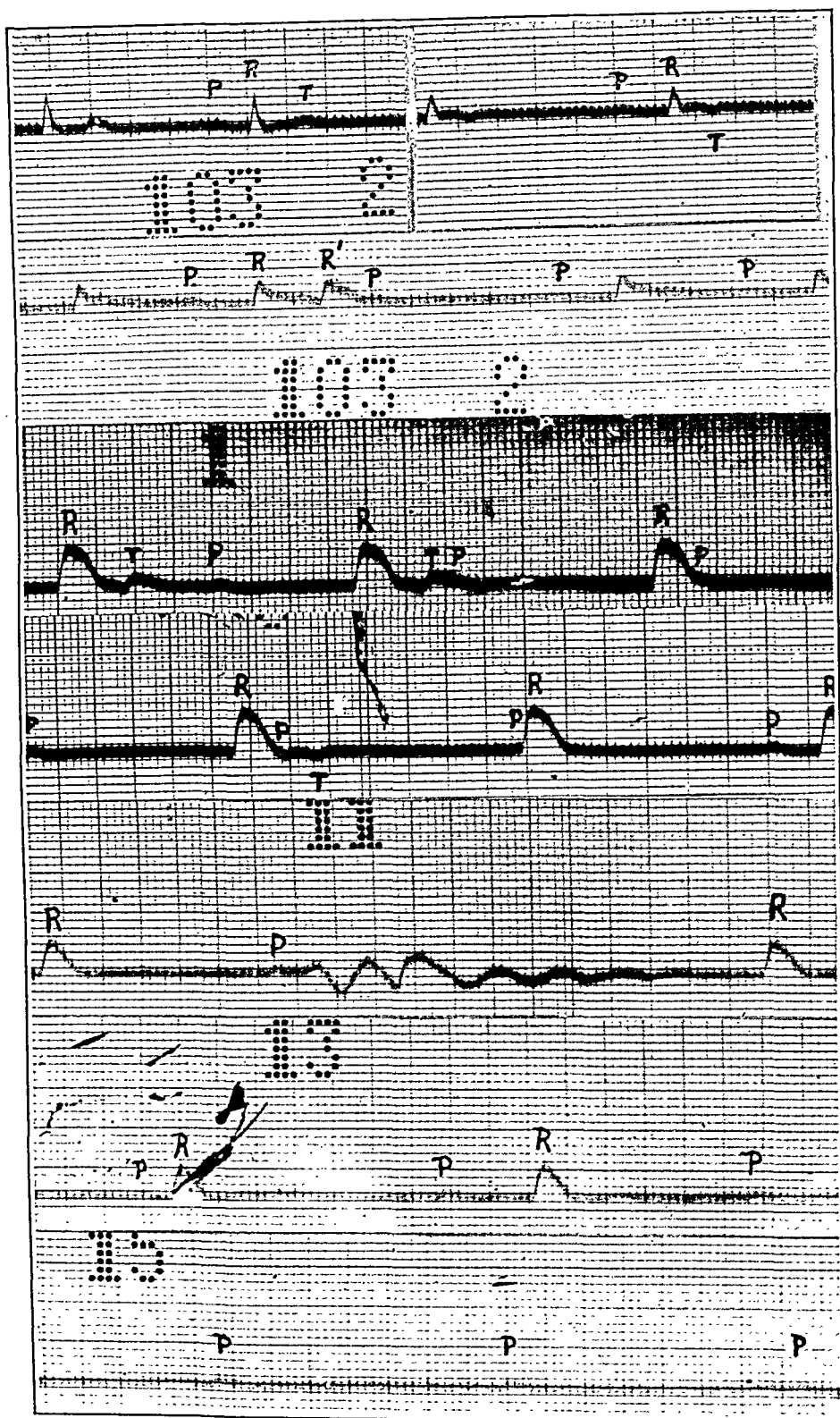


FIG. 3.—Sequence of prints of the dying heart in Case III, analyzed in the text.

activity manifested for some time. This is the final evidence of energy development in the heart.

Summary and Discussion of Case III. Summarized, the sequence of events was as follows: (1) Progressive sinus slowing and arrhythmia; (2) increased conduction difficulty; (3) inversion of the *T* wave; later it disappeared or became isoelectric; (4) one ventricular extrasystole; (5) complete auriculoventricular dissociation; (6) widening of the *QRS* wave; (7) momentary ventricular fibrillation; (8) regular auricular activity manifested for some time after cessation of all ventricular activity.

The importance of ventricular fibrillation clinically has recently been emphasized. Experimentally, it may be produced quite regularly in advanced digitalization of the heart by warming rather limited portions of the ventricle. Under digitalis the ventricle tends to assume independent automaticity and localized warming of the musculature produces a marked increase in the irritability of that part. Upon cessation of the warming, feeble irregular contractions or coarse undulations may occur.¹⁹

Ventricular fibrillation is a terminal phenomenon. One case is recorded, however, in which the heart recovered for a short time after ventricular fibrillation was shown by the electrocardiogram to have taken place.²⁰

CASE IV.—F. E., aged sixty-six years, suffered from diabetic gangrene and general arteriosclerosis. The heart was negative. Soon after admission and toward the end of her illness, there was no glycosuria and no acidosis.

The urine showed a moderate amount of albumin and many hyalin casts. The blood Wassermann test was negative. The blood chemistry showed an excess of creatinin, 3.1 mg. per 100 cc.

Course: The temperature was normal except for a rise to 105° F. with terminal coma.

Diagnosis: Diabetes, gangrene right foot, general arteriosclerosis.

Electrocardiographic Studies (Fig. 4). One record was taken twelve hours before the patient died. This showed tachycardia, slightly less than 150 per minute. At first there was marked left ventricular preponderance and slight inversion of the *T* wave in Lead I.

Shortly before death there was atrial slowing to a rate of about 60 per minute with slight arrhythmia. This was associated with the following peculiarities as illustrated in the sequence of prints in Fig. 4.

The *P* wave is at first very small and diphasic with a tendency to inversion. Its absence is frequent showing intermittent failure

¹⁹ Schlomovitz: *Am. Jour. Physiol.*, 1921, 55, 485.

²⁰ Robinson and Bredeck: *Arch. Int. Med.*, 1917, 20, 725.

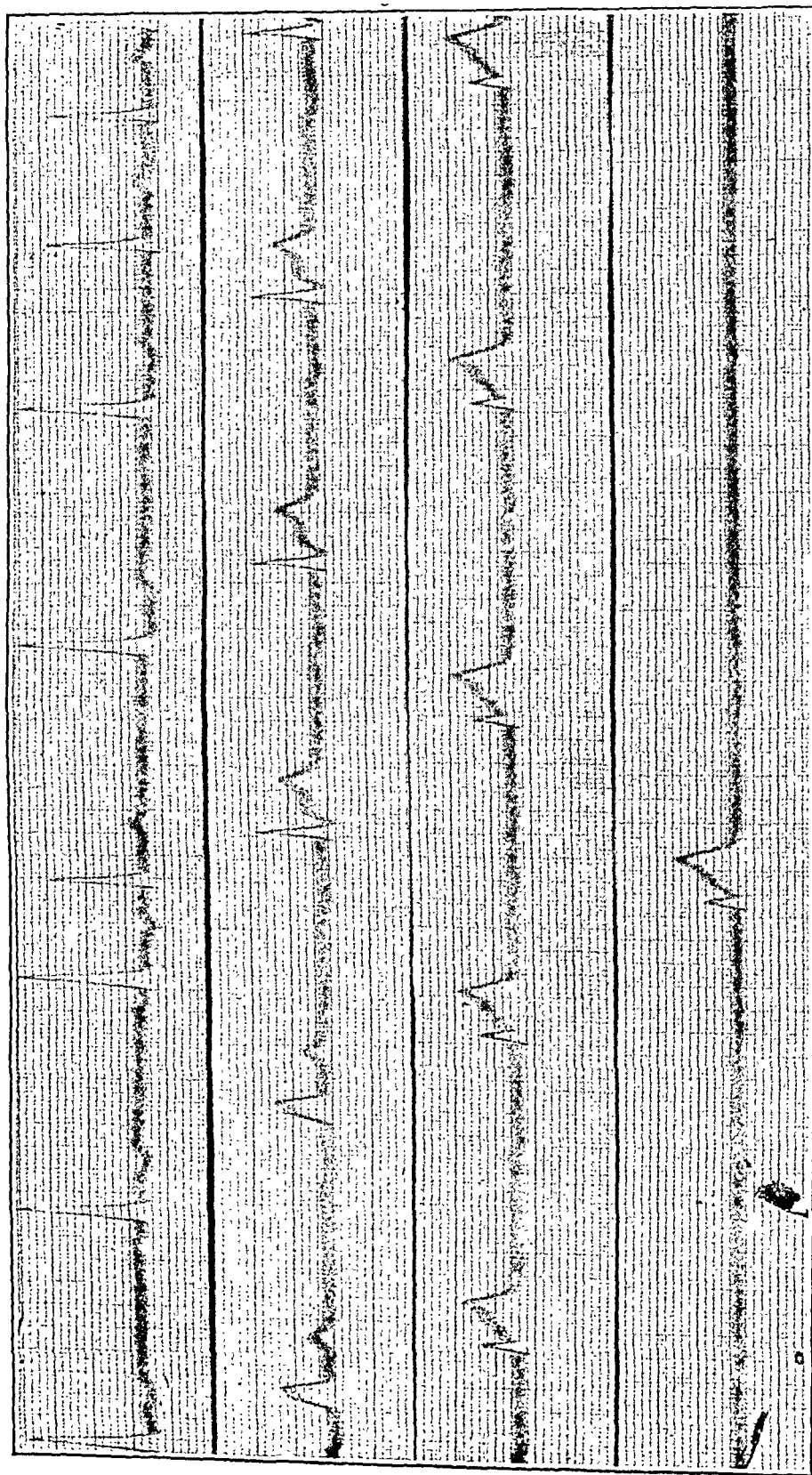


FIG. 4.—Sequence of prints of the dying heart in Case IV, analyzed in the text. Abscissæ 1 division = 0.02 second. Ordinates 1 division = 10^{-4} volts.

of the sinus node. When it does occur, it is followed without any impairment of *P-R* conduction by a ventricular cycle. The ventricular cycles occur in two distinct forms. One is higher in voltage and wider than the other. In this cycle, the *T* wave is diphasic, its first and main portion sharply inverted (*a*). This larger form of wave changes rapidly and becomes lower in amplitude and wider with marked notching and thickening and finally disappears (*b*).

Before this happens, however, its *T* wave has become upright. The other form which appears more normal and occurs with about equal frequency and irregularity at first, takes place occasionally also in response to a sinus stimulus. It gradually diminishes in voltage while its upright *T* wave increases in height. This last form of curve makes up all the ventricular cycles of the last portion of the record.

Conduction defect increases after the sinus has recovered, to a *P-R* interval of 0.45 second. Finally there is complete auriculo-ventricular dissociation. The last ventricular cycle is seen in strip *d*. After that auricular impulses are visible for several minutes at a regular rate of about 43 per minute.

Summary of Case IV. The sequence of events was as follows: (1) Sinus failure; (2) impaired or abnormal intraventricular conduction of many of the ventricular beats; (3) recovery of the atrial node; (4) progressive conduction defect; (5) complete auriculo-ventricular dissociation and (6) terminal auricular activity after the last ventricular cycle.

CASE V.—A. F., aged twenty-seven years, was a case of epidemic encephalitis.

The patient's last illness began five weeks before her death with severe continuous frontal headaches and abdominal cramps. She was feverish and dizzy when moving about with diplopia and drowsiness. At times, she spoke irrationally.

Physical examination showed ptosis of the right upper eyelid. The pupils did not react to light. The heart was not enlarged and there were no murmurs.

The urine showed a moderate amount of albumin and no casts. The Wassermann test was negative both in the blood and spinal fluid. The temperature was 100° to 101° F. throughout.

Course: Several days before death, the patient lapsed into coma and developed left hemiplegia. She died with marked cyanosis and cardiac failure.

Diagnosis: Epidemic encephalitis.

Electrocardiographic Studies (Figs. 5 and 6). The routine electrocardiogram in this case showed tachycardia with a rate of 150 per minute, left ventricular preponderance and high *P* and *T* waves in Lead II. The *S-T* phase exhibited what is probably a marked spiratory effect.

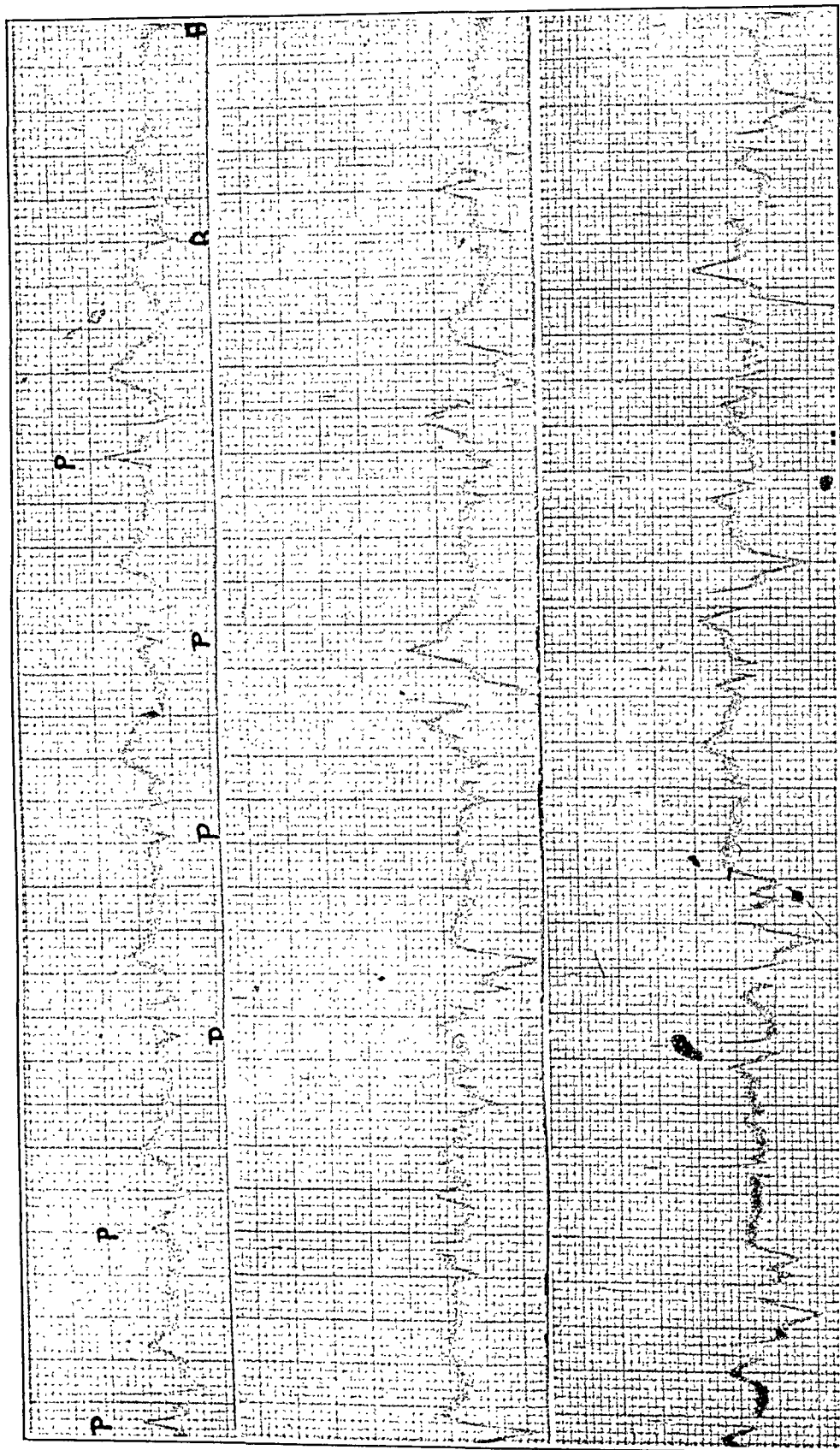


Fig. 5.—Sequence of prints of the dying heart in case V, analyzed in the text.

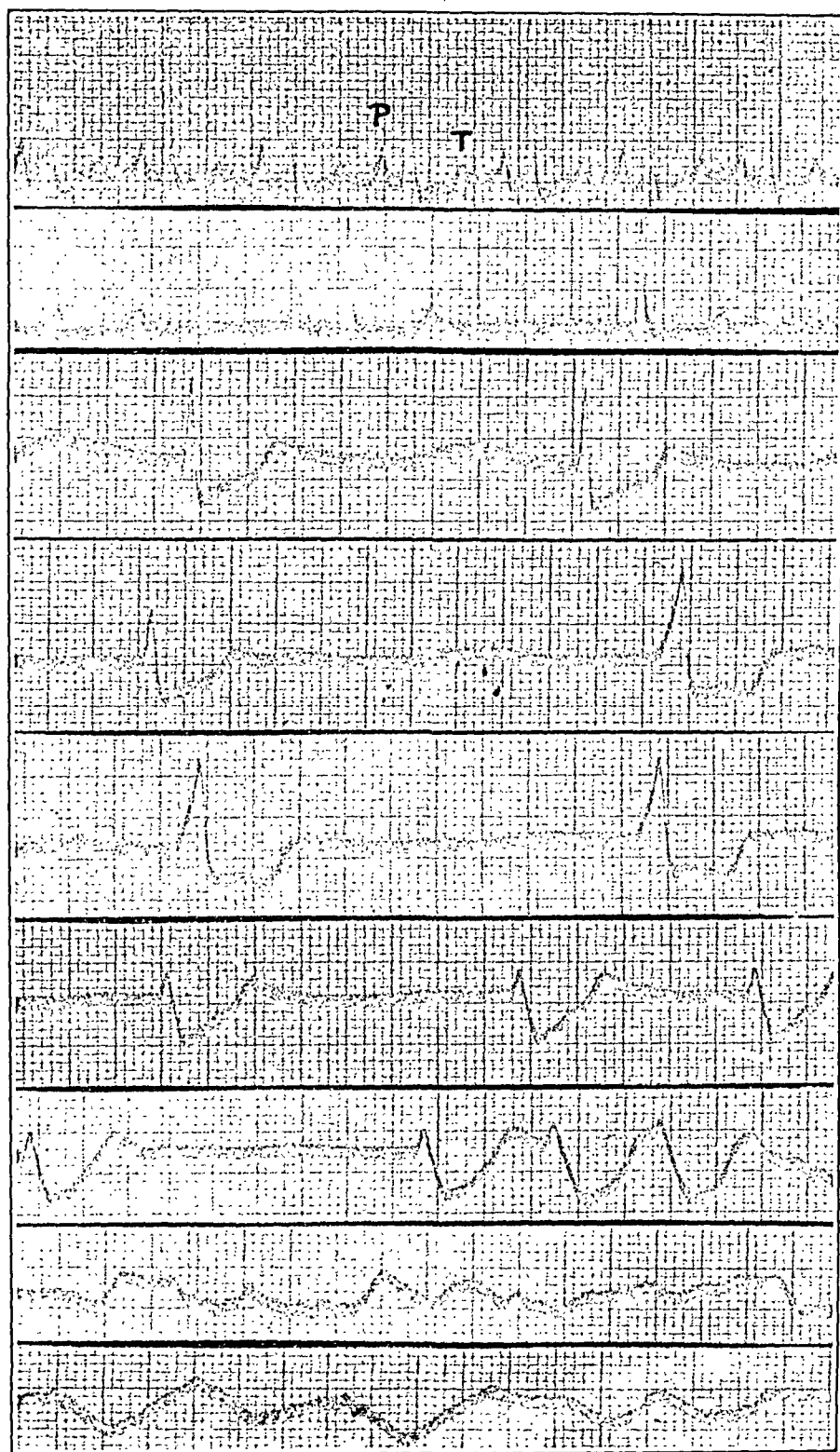


FIG. 6.—Sequence of prints of the dying heart in Case V, analyzed in the text.

The atrial slowing later became more marked. The *P* wave also became more acute. Suddenly, in one cycle, its amplitude diminished; then followed a remarkable inversion of the *P* wave for three cycles. The normal *P* wave recurred once, after which it was replaced by the inverted type of curve. The *P*-*R* interval, however, remained the same. This is quite remarkable and demands some discussion (Fig. 5a).

As the record progressed, however, nodal rhythm and nodal tachysystole became marked. Frequent ventricular extrasystoles of various types arising from various parts of the heart interrupted the record at every few cycles (Fig. 5b-c). These show no complete compensatory pause.

After a time, the normal form of the *P* wave with its previous *P*-*R* interval was again seen (Fig. 6a). The normal sinus rhythm without any extrasystoles returned and it is with this type of mechanism that the heart progressively died. This is shown in Fig. 6 taken in Lead II.

The sinus rate is slow, 50 per minute, with a *P*-*R* interval of 0.16 second and a small normal appearing *T* wave (Fig. 6b). Suddenly the *P* wave becomes prolonged and undulating, extending over a period of about 0.6 second, followed by an upright *QRS* wave with an abnormal *S*-*T* phase (Fig. 6c).

The long undulating *P* wave gradually becomes inverted, and then again returns to an upward curve but with much greater prolongation of the *P*-*R* period. The auriculoventricular interval is now more than one second (Fig. 6d). Suddenly the *QRS* wave becomes much widened; the *T* wave becomes inverted (Fig. 6d), and gradually the amplitude of *QRS* diminishes and complete dissociation of the auricles and the ventricles takes place (Fig. 6f).

After much nodal depression or slowing, the ventricle suddenly goes into fibrillation (Fig. 6g). For a period, however, waves occur with more or less regularity, at times slower and at times faster having a contour of terminal ventricular curves observed in other cases. After the last distinct ventricular wave, there is a prolonged isoelectric period after which there is a sudden irregular sequence of waves for several seconds terminating in the cessation of all heart action.

Summary and Discussion of Case V. Summarized, the sequence of events may be stated as follows: (1) Atrial slowing and sudden inversion of the *P* wave; (2) frequent ventricular extrasystoles of various types; (3) nodal rhythm and nodal tachysystole with frequent extrasystoles; (4) loss of sinus control; (5) recovery of sinus control; (6) atrial slowing; (7) rare form of *P* wave with extreme conduction defect; (8) change of *QRS* wave to abnormal widening; (9) deformity of *T* wave; (10) ventricular fibrillation; (11) partial ventricular recovery; (12) terminal fibrillatory waves.

Inversion of the *P* wave, which is strikingly seen in the first strip of Fig. 5, demands some discussion. Analyzing our data, we see first a high pointed *P* wave with a *P-R* interval of 0.12 of a second. This interval is not appreciably changed in any of the succeeding abnormal *P* waves, which would mean that the pacemaker was located in the sinus region. What is it then, that causes the inversion of the auricular wave?

We know that due to vagus influences, the form and height of the *P* wave may be changed. It may become negative, diphasic or small. These changes, it is also known, are not synchronous with changes in the ventricular curves. They are also not synchronous with inspiration and expiration.¹ It is upon this basis that the only explanation is forthcoming. This is especially the case as there are other manifestations in this electrocardiographic record that indicate vagal influence.

The contour of the *T* wave as is well known bears a close relation to the change in the direction of the conduction stimulus. This is illustrated especially in strip *d* of Fig. 6. In this strip, the first cycle is of one form and the second is of another form, in which conduction defect and inversion of the *T* wave has developed.

The rare abnormality and deformity of the *P* wave which takes place in strips *c-d* of the record requires explanation. A slow undulation, extending over a period of 0.6 second and bearing a regular relation to the ventricle, must necessarily be explained as due to auricular activity. It occurs with regularity in definite relation to the *QRS* wave. The *P-R* interval increases progressively. It is probable that both the abnormal wave and the increasing block are due also to vagal influence.

CASE VI.—J. V., aged seventy-five years, was ill with bronchopneumonia one week before he died.

Physical examination revealed distant heart sounds of poor quality. The lungs were emphysematous and there was bronchopneumonia of the right lower lobe.

Course: The temperature was 101° F.; the terminal temperature was 100° F. The patient died with pulmonary edema.

Diagnosis: Bronchopneumonia.

Electrocardiographic Studies. Just before the patient died, the electrocardiogram showed left ventricular preponderance. The *P* wave was high. The *QRS* wave was notched at the apex in Lead II and in the ascending limb of Lead III.

The dying heart showed a complete change of mechanism with sinus failure and entire absence of the auricular wave. Later it returned, but in a very peculiar form. There was a slow, rounded curve of low amplitude and delay in conduction of 0.4 second. A short period later, the dissociation was complete. Fibrillatory waves

¹ Einthoven, Fahr and De Waart: Arch. f. Physiol., 1913, 150, 275.

occurred at the end after the last ventricular contraction. Throughout the terminal part of the record, the ventricular curve is bizarre (Fig. 7).

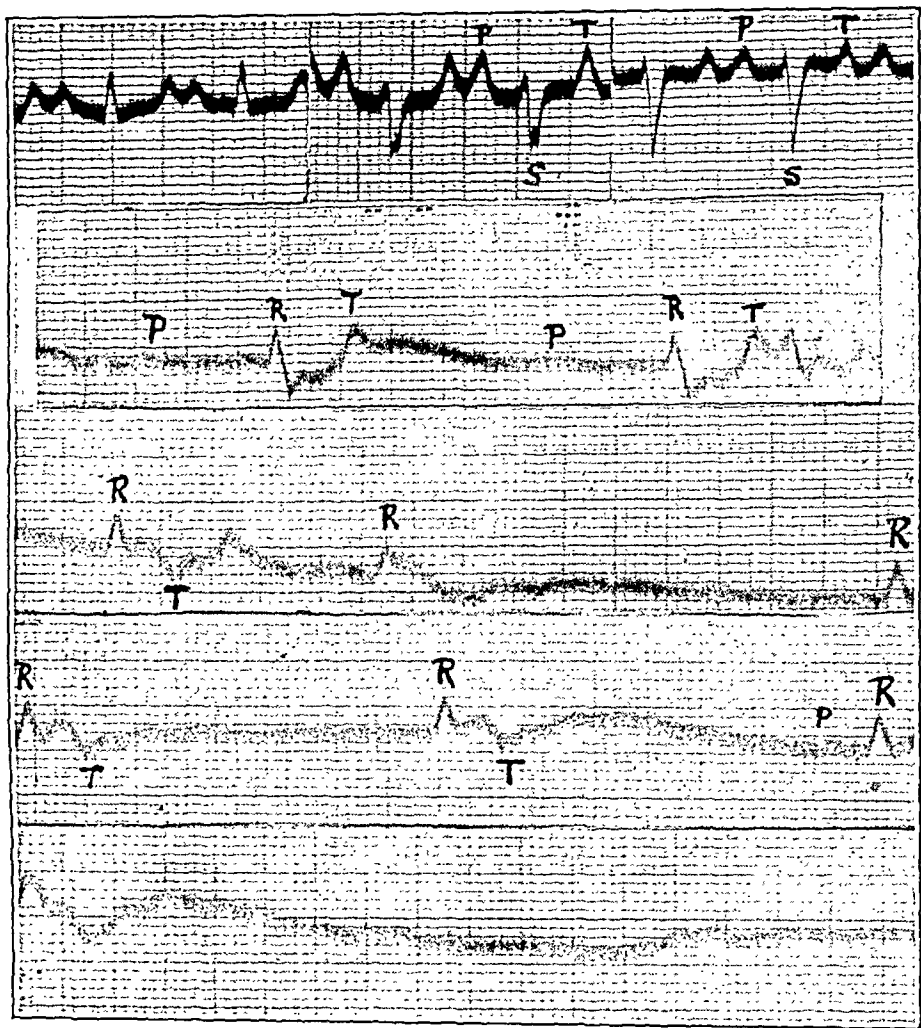


FIG. 7.—Sequence of the prints of the dying heart in Case VI, analyzed in the text.

CASE VII.—F. L., aged sixty-three years. The patient had suffered for seventeen years from frequent attacks of tonsillitis and rheumatism. For two years prior to her death, she had dyspnea, palpitation, nasal hemorrhages, hemoptysis, cyanosis, swelling of the legs, polyuria and nycturia.

Physical examination revealed cyanosis, dyspnea and orthopnea. The heart action was irregular with a pulse deficit of 18. There was a diffuse apex impulse and a systolic thrill in the sixth space.

The first sound was impaired and the pulmonic second sound was accentuated. The liver edge was felt below the level of the umbilicus and there was marked edema of the extremities.

The urine showed a large amount of albumin and the blood a moderate secondary anemia. The temperature was normal.

Course: Right hydrothorax and increasing cardiac decompensation developed. Toward the end, the pulse became very weak and slow. Adrenalin, m xv, was given hypodermically fifteen minutes before death.

Diagnosis: Auricular fibrillation. Right hydrothorax.

Electrocardiographic Studies. About two weeks before the patient died, the electrocardiogram showed auricular fibrillation with extreme tachycardia. There was right ventricular preponderance and occasional left ventricular extrasystoles. Just preceding the patient's death, there was marked slowing of the rate. The *S-T* phase in Leads II and III became depressed and markedly rounded and *T* was slightly above the isoelectric level in all three leads. The *QRS-T* cycle became much prolonged and there were occasional left ventricular extrasystoles of the same form as before. That heart-block and auriculoventricular nodal control of the ventricular rhythm took place during periods is evidenced by the comparative regularity of the beats.

Another record was taken five minutes after the patient was considered clinically dead, that is, after the heart had stopped beating audibly. In this, three slight indeterminate waves were seen which occurred at regular intervals from each other and of indefinite conformation.

Summary and Discussion of Case VII. Summarized, the sequence of events was as follows: (1) Slowing of rate; (2) lowering of *T* wave in Lead I; (3) *S-T* phase more rounded and curved in Lead II with prolongation of the entire time of the *QRS-T* cycle and right ventricular extrasystole seen; (4) complete block with assumption of nodal rhythm.

Prolongation of the *S-T* phase was evident and does not seem, in this case, to bear a direct relation to bundle branch defect. The studies that have heretofore been made on the significance of this prolongation indicate that the variation in the length of the *S-T* interval is more dependent on cardiac rate than on any other factor. It is not a constant accompaniment of any other phenomena of the electrocardiogram.²¹

General Summary and Conclusions. Seven electrocardiographic studies of the dying heart are reported. Three of the cases died from heart disease and the other cases from other illnesses. One of the three presented auricular fibrillation during life.

In all the cases, the first and main effect was failure of the sinus control of the heart action, with assumption of control by the auriculoventricular node. This is without doubt the most significant

²¹ Buchanan: Arch. Int. Med., 1921, 28, 484.

phenomenon in terminal heart activity. It is also in correspondence with the significant findings under experimental conditions.

The cessation of the normal auricular contraction stimulus seems to be the critical phenomenon in the process of death. Before this happens, the sinus node shows irritability and depression in various sequences and degrees and it is probable that if the disturbance could be controlled before cessation of sinus function, recovery of the heart might occur. After this happens, it is known experimentally that the heart will not recover although reoxygenated.

The simultaneous control by two centers of the heart's rhythm is definitely a sign of poor prognosis. It signifies sufficient depression of the sinus control to permit the auriculoventricular node to dominate the rhythm.

From a functional standpoint, it is obvious that this must lead to serious impairment of the circulation. Simultaneous auricular and ventricular contractions will frequently take place. Inadequate filling of the ventricles is the inevitable result when auricular contractions occur without any relation to the ventricular beats. No possible functional adaptation can take place between the upper and lower chambers.

Although ventricular extrasystoles are a common occurrence in the dying heart under experimental conditions, they were encountered in only 2 of the cases here reported. In 1 of the cases, they existed long before death and in the other case they occurred suddenly from various points in the ventricular muscle just at the time vagus effects were most notable, suggesting vagus influence as the cause.

Of course, a functional defect in conduction throughout the ventricle is apparent in most instances; it is due either to dromotropic influence through the vagus depressing conduction, or to nutritional disturbances of the conducting mechanism.

Ventricular fibrillation occurred in 2 cases. In 1 instance, it was only momentary and in the other more prolonged. In both, this was followed by a very short period of recovery of rhythmic ventricular action, but without any regularity. The ventricles stopped beating before the auricles in 3 cases. In the other 3, auricular action ceased first. It is usual in the human dying heart that the electrocardiogram will continue to show evidence of activity without there being any visible or audible evidence of ventricular systole.

As a result of this study, we want to call attention to the greater importance of the earlier phenomena in the auricles as compared with those which occur later in the ventricles, when the conditions are beyond recovery. We say this in view of the findings in a large number of other cases to be reported in which the early criteria were used in a study of their prognostic significance.

The emphasis upon the earlier disturbances of auricular action

are important, since intracardiac injections of epinephrin and other stimulants may be of life-saving value and since it has not yet been ascertained in what period in the process of death of the heart their value may prove greatest.

In correlating our findings with those of the two or three previous clinical studies on this subject, we feel that one is justified in considering change in height, direction and contour of the *S-T* period and the *T* wave as the only change encountered in every case, but this is more or less of a very late phenomenon.

In 1 of our cases, the *QRS* wave (Fig. 2) underwent almost no alteration. The changes that did affect the *QRS* wave in some instances, that is, lowering of voltage and widening and notching, are explained on the basis of intraventricular conduction defect. The changes taking place in the *T* wave have thus far eluded positive interpretation.

We want to express our thanks to the attending physicians of Beth Israel Hospital for permission to study these cases. We also want to thank Mr. Nicolai Opolonick for his technical assistance.

THE SURGERY OF PULMONARY TUBERCULOSIS.*

BY JOHN ALEXANDER, M.A., B.S., M.D.,

ANN ARBOR, MICHIGAN.

(Continued from July and August, 1924)

THE following always use regional and local anesthesia: Jessen, Ranzi, Shivers (in 5 of 20 operations he was obliged to add gas or ether), A. Christensen (without morphin), Willy Meyer, Eloesser, Ochsner and H'Doubler. Stöcklin and Schreiber used it upon 98 of 100 patients. Bérard prefers a combination of regional-local anesthesia and light general narcosis with ethyl chloride or nitrous-oxide-oxygen for one-stage operation upon patients whose expectoration is less than 60 to 80 cc a day. If the expectoration exceeds this, or if the operation is to be performed in two stages, he tries to operate entirely under regional-local anesthesia.

Archibald, Welles, Hedblom and Gravesen prefer to combine novocain-adrenalin and light nitrous-oxide-oxygen anesthetics, as less of each is needed, and dangerous symptoms may be expected from neither. Shortle and Gekler, Riviere and Romanis, and Willard Smith prefer nitrous-oxide-oxygen alone.

Sauerbruck, Saugmann, Bull, Davies prefer ether alone if the daily amount of sputum is small, and general narcosis may be necessary if the patient is extremely apprehensive, or greatly frightened by hearing the ribs cut, or by a sensation of "tightening"

as the chest narrows. Sauerbruch thinks that ether contributes less toward shock than does local anesthesia.

In order to minimize the postoperative pain some surgeons interrupt the intercostal nerves as far posteriorly as possible. Davies, Eloesser and Hedblom inject a few drops of absolute alcohol into each nerve; Nyström crushes the nerves and injects alcohol. Jessen, Schreiber and Mühsam resect 1 to 2 cm. of each nerve, sometimes together with a section of the overlying periosteum. Sauerbruch resects 1 to 2 cm. of each nerve in those patients whose periosteum is thick and edematous, as he has learned that, otherwise, they are liable to suffer from intercostal neuralgia. For many months there is total anesthesia in the nerve distribution, and then gradual compensation takes place by an overgrowth of neighboring nerves. Paralysis of the abdominal wall on the operated side has not proven harmful, although, on theoretical grounds, it would seem that coughing would be less effective, and that the bulging permitted to the costal border might remove a valuable place of counter-pressure for the collapsed posterior chest wall.

IX. Sauerbruch's Extrapleural Paravertebral Thoracoplasty. This operation may be considered a compromise between the extensive resections of the old Brauer-Friedrich technic and the narrow, columnar resections of only the upper seven or eight ribs of the earliest Wilms operation. Although only short lengths of ribs are removed, the resections are so placed as to obtain relatively great lung compression, and the clinical results are better than with any other technic, except possibly Brauer's modification of it. When skilfully performed it causes little operative shock, and rarely upsets respiration or circulation, and the resulting deformity is slight. It is the technic, although sometimes slightly modified, that is being used throughout the world by surgeons of greatest experience.

Position on Operating Table. The patient lies on the better side with both thighs flexed; a cushion is placed under the loin, another beneath the thighs is held firmly with a strap to prevent the patient from slipping. The upper half of the table is raised 30°. If a patient is orthopneic he sits across the table and leans forward on the shoulders of an attendant. Saugmann always used the sitting posture; Bérard does when using local anesthesia.

Incision. Provided the upper lobe is the more diseased, ribs XI to V are removed first, through a hook-shaped incision which commences 6 cm. from the fourth vertebral spine and runs straight down to the tenth rib, when it curves forward to posterior axillary, or midaxillary line (see Figs. 6 and 14). Jessen finds that an incision making an angle of 120° at the tenth rib is more convenient than the Sauerbruch "Bogenschnitt." Ostermeyer recommends a large Z-shaped incision which cuts the pectorals and subclavius, and loosens the serratus magnus and the latissimus, on the grounds that

there is less hemorrhage and that there is better protection of nerves and vessels. I believe that any such advantages would be offset by the greater operative shock and exposure of larger raw surfaces to the danger of infection, and by the fact that more than a safe amount of local anesthetic would be necessary. Towels clipped to

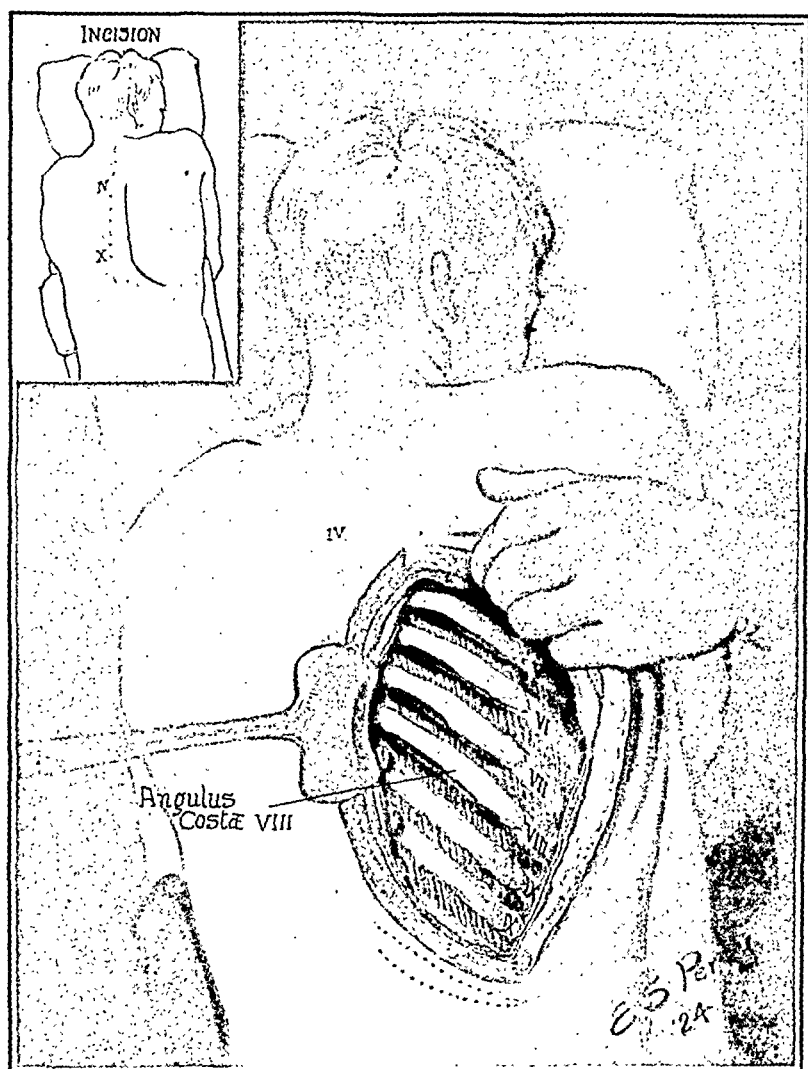


FIG. 6.—First stage of a Sauerbruch paravertebral thoracoplasty. The erector spinæ muscles have been detached from the angles to the necks of the ribs and retracted. Ribs XI to V inclusive have been stripped of their periosteum for the requisite distances; ribs XI, X and IX already have been resected. The scapula is being retracted by the hand.

the skin edges immediately after the skin incision is made constitute a wise precaution against wound infection.

After the lower ribs have been exposed they are best removed in this order X, IX, VIII, VII, VI, V, XI. If it is then decided to complete the operation, instead of dividing it into two stages, the

wound is packed with gauze and the incision continued straight up to the neck, and curved forward to the anterior edge of the trapezius. During the latter part of its course it will sever two medium-large arteries—branches of the suprascapular and of the transverse colli. Strong retraction in the angle of the wound affords an excellent view of the first rib. The upper four ribs are resected from below upward. The muscles and skin are sutured with interrupted stitches, using two layers for the heavy scapular muscles. A long rubber drain is inserted beneath the muscles, and emerges from the lower end of the incision.

In case the operation is divided into two stages it is not necessary to reopen, at the second operation, the incision originally made for resection of ribs XI to V. Incision for the second stage curves from the anterior edge of the trapezius down to the base of the neck posteriorly, 6 cm. distant from the vertebral spinous processes, and then runs vertically downward to the seventh rib, where it is made to curve forward around the angle of the scapula, thereby allowing the scapula to be displaced well forward to expose the ribs beneath it (see Figs. 7 and 14).

The ribs are usually removed subperiosteally. When pleura and periosteum are seen to be much thickened and inflamed, Sauerbruch removes the periosteum in order to prevent early regeneration of bone that would check the progressive narrowing of the chest that is expected to occur during many weeks, and also resects 1 to 2 cm. of the intercostal nerves to prevent postoperative neuralgia. Jacobaeus and Key and Nyström also remove the periosteum. Jessen favors rib regeneration as affording advantageous fixation of the chest wall; he removes rib sections at operation long enough to make secondary narrowing of the chest unnecessary; he does not section the nerves as they are important for the nourishment of the tissues and for the stability of the weakened chest wall. Bérard fears that resection of the periosteum might complicate the operation by wounding the pleura, intercostal vessels and nerves. As prophylaxis against deformity Hug urges that great care be taken of the motor nerves, and of the erector spinæ and latissimus dorsi and trapezius muscles, as avoidance of kyphoscoliosis is largely dependent upon their strength and function.

Unless the ribs are very close together it may be found convenient to strip each rib of its periosteum before removing any of them; if this is done, gauze should be tucked beneath the ribs in order to steady the freed lung which is seen moving rather violently with respiration, but in a paradoxical sense, beneath the bare ribs (Welles).

The skill employed in resecting the ribs largely determines the time consumed by the operation, the amount of operative shock and postoperative pain. A longitudinal incision is made in the periosteum, which is then readily pushed away from the lateral

flat surface of the rib with a gauze sponge or ordinary periosteal elevator. At both the upper and lower edges of the rib, under the attachments of the intercostal muscles, the periosteum is usually toughly adherent, and its detachment with the commonplace elevators is time-consuming, and unless done with due care, may

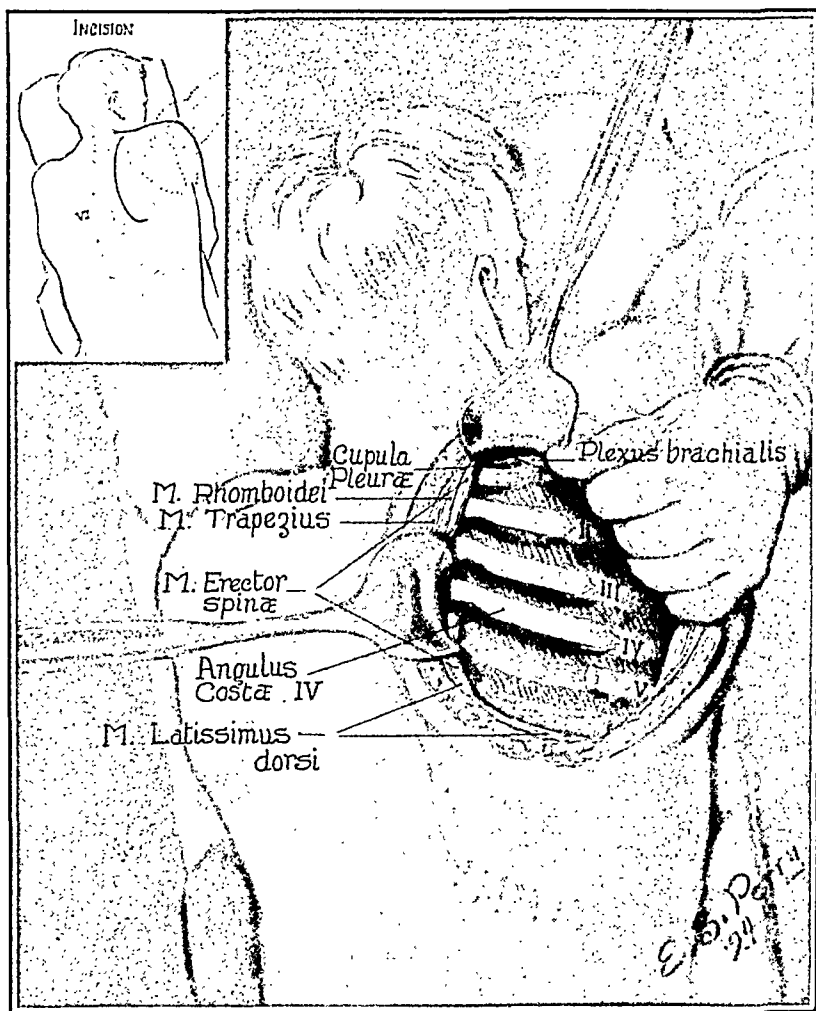


FIG. 7.—Second stage of a Sauerbruch paravertebral thoracoplasty. Ribs IV to I inclusive have been stripped of their periosteum for the requisite distances, and are about to be resected from below upward. The stumps of ribs V and VI, which were resected during the first stage of the operation, appear in the bed of the scapula.

tear the pleura. It should be remembered that its detachment here is somewhat simplified if the surgeon always works from before backward on the lower rib edge, and from behind forward on the upper rib edge. I have recently designed an instrument* that accomplishes this difficult step in thoracoplasty neatly and with

* Manufactured by George Tiemann & Co., 107 East 28th St., New York City.

very great saving of time, and without danger to the pleura. After the rib edges are freed of periosteum the Doyen raspatory is used to separate the periosteum from the posterior surface of the rib. The freeing of the rib posterior to its angle may prove very difficult, as here it is covered with the tough attachments of the erector spinæ muscles; it is best accomplished with a very sharp periosteal elevator, curved on the flat, this being used to cut and scrape away these attachments. Sauerbruch often removes the periosteum with the rib posterior to its angle, but takes care not to wound the pleura or intercostal vessels and nerve.

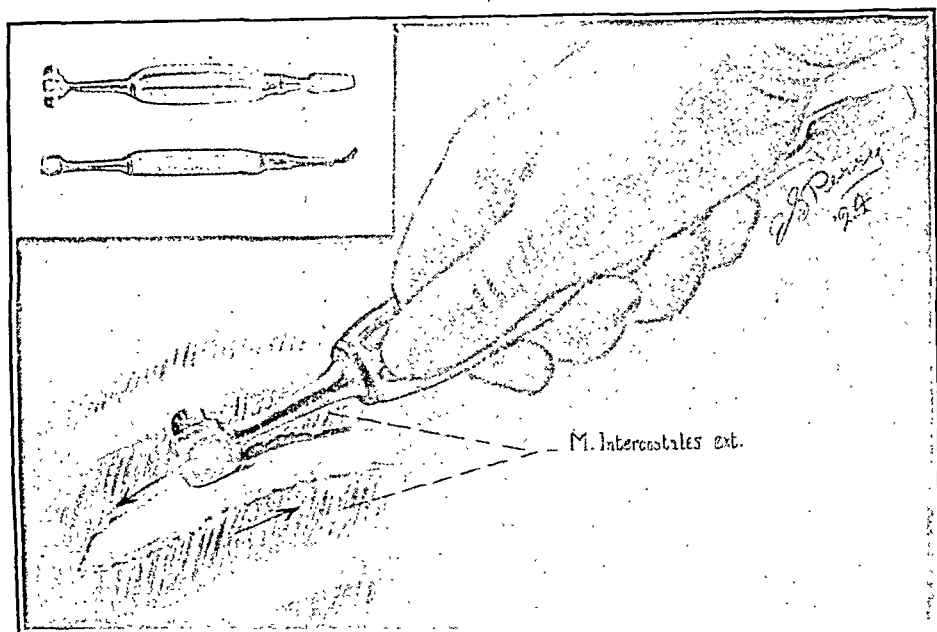


FIG. 8.—Author's rib-edge periosteum stripper in action.

The rib is sectioned with a rib shears, first anteriorly, then posteriorly (beneath the broad erector spinæ mass, which first must be dissected from the ribs), as near to the transverse process of the vertebra as possible. Saugmann recommends cutting the second and third ribs in their middles if they are very hard to reach, and then, by elevating each segment, the anterior and posterior sections may more easily be made. The double lever type of rib shears is much to be preferred to the commonplace ones which frequently cause fatigue-cramp of the surgeon's hand after two or three ribs have been cut. A special shears with a long neck is very convenient for the deep-lying first rib. As it is very difficult to resect the ribs as far as the transverse processes with these bulky instruments, it is frequently necessary to shorten the posterior stumps with *rongeurs*. Schreiber has at times removed parts of the transverse processes in an attempt to lessen the capacity of the costovertebral

gutter in order to obliterate large cavities. The distance between the vertebral bodies and the transverse processes is from 4 to 5 cm.

Sauerbruch's highly trained team's operating time is from ten to twelve minutes. He does not say whether this is for a complete operation or for one of two stages, but it does include the whole operation, from incision to skin suture. He believes that speed is an important factor in operations upon tuberculous persons. Jessen can do the complete operation, ribs XI to I, in twenty minutes. Bull's average time, with one or two assistants, is one hour. Either stage of the operation may be performed handily by a well-trained team in forty minutes.

Lengths of Ribs Resected. Sauerbruch's average resections are as follows: rib I, 3 cm.; II to V, 6 to 8 cm.; VI to VIII, 12 to 15 cm.; IX to XI, 12 to 6 cm.; total about 110 cm. While using Sauerbruch's technic, most surgeons of broad experience with thoracoplasty resect greater lengths of rib. Sauerbruch himself is frequently obliged to resort to secondary operations because the pulmonary compression obtained by the first one is not sufficient to control the disease. Shivers removes more rib than Sauerbruch, and is gratified with the results and rarely needs to operate secondarily.

The old Brauer-Friedrich operation took from 130 to 200 cm. of ribs. Bull averages 120 cm., and has removed as much as 150, 160 and 183 cm., the maximum resections being reserved for predominantly caseous lesions, for stiff-walled cavity or bronchiectatic types, for severe hemorrhage cases and for great traction displacements of the mediastinal structures. Saugmann averaged 134 cm., his limits being 80.5 cm. and 172 cm. Jacobaeus and Key average 140 cm. The Stöcklin-Schreiber limits are 110 and 140 cm., relatively great lengths being resected from the upper ribs according to the Brauer technic, which will be described below. Lorey has taken 175 and 180 cm. by the Brauer technic; Brauer himself averages only 125 cm.

The first rib must be resected, or at least divided, for efficient pulmonary compression, as the chest "hangs" on it; it is, as Bérard says "the key to the thoracic dome," the settling of the whole hemithorax that follows its section is practically necessary for the obliteration of apical cavities. Surgeons are almost unanimous about this. Unfortunately it was the early practice of some surgeons to leave it untouched, because of the difficulties of reaching it, and the possible dangers of injuring the subclavian vessels and the brachial plexus, which are in intimate proximity with the rib. It may be left intact only when the apex is so shrunk as to have sunk beneath it to the second rib (Sauerbruch; Madinier); or, as Bull says in opposition to Sauerbruch, if the apex is free of disease. If the first cartilage is very pliable, simple division may suffice; a 3 to 5 cm. resection of the posterior extremity is considered satisfactory; attempts to remove greater lengths threaten injury to the vessels and nerves.

The Eleventh Rib. Brauer and Saugmann see no advantage in resecting this rib. Bull, Sauerbruch, Baer and almost everyone else remove it for the reason that the diaphragm thereby loses some of its bony support and rises into the chest and assists in compression of the lung; also diaphragmatic movement is somewhat impaired and this adds to the pulmonary rest.

The Clavicle. Twelve years ago Wilms occasionally removed a small section of the clavicle to allow the weight of the shoulder to assist in the compression. More recently Eloesser has resected from 2 to 8 cm. and sutured the Z-shaped incision in the bone with kangaroo tendon. This procedure has not gained favor because it causes considerable deformity, and because it has not been shown to be particularly efficacious; the weight of the shoulder tends to fall forward rather than inward.

Interruption of Operation. The question as to whether complete thoracoplasty should be performed in one or several stages has been much debated. It should be recalled that, in any event, the less diseased lobe must be operated upon first in order to prevent aspiration when the secretion producing lesions are compressed. While agreeing with this, Brauer calls attention to the fact that this order of operating does not absolutely assure against aspiration.

The advantages of the two-stage operation are: (1) Less shock and less sudden changes demanded of the circulatory and respiratory mechanisms, which are enabled to adjust themselves gradually. Since Jessen has been using two stages he no longer sees the acute disturbances of circulation and respiration, and no longer is forced to use stimulants. Bérard favors the one-stage operation; he has been fortunate in having had no immediate operative deaths; his patients, however, experience two or three very stormy and dramatic postoperative days; great pain and dyspnea and difficulty in expectorating, cyanosis, high pulse and temperature, and sometimes anginoid or asphyxial attacks as a result of mediastinal displacement. (2) Fewer toxic products are pressed into the general circulation to endanger latent lesions in the better lung; therefore two stages are important if the better lung is under suspicion of activity. (3) The first stage usually causes enough rest and relaxation of the lesions to bring about a definite clinical improvement, which betters the chances of success of the second stage. Nine of 36 of Schreiber's patients were distinctly improved during the two or three weeks following the first stage, and two of them, one with a cavity, became entirely cured without necessity for the rest of the operation! Jessen speaks of the marked improvement in general condition, and in some cases in lesions of the better apex, following the first stage.

The advantages of the one-stage operation are: (1) Much preferred by the patient. (2) Risks of embolus, and anesthetic poisoning, and of wound infection run only once. (3) If wound infection should occur the whole lung has been compressed—no need to post-

pone a final stage of the operation. (4) Muscles are sectioned only once. (5) More even lung compression, and so less irritation of cavities and fewer chances of lung hemorrhage. The scapula fits more evenly against the lung (Gravesen).

It follows that every case is a law unto itself, and that it may be found advisable to interrupt an operation that was commenced with the intention of completing in one sitting. Hauke reports a one-stage operation during which the patient's condition was excellent and did not suggest interruption of operation; twelve hours later came paradoxical respiration, dyspnea, cyanosis and small pulse. It is important to realize that it is usual for the pulse to be 120 or more, and the respiration 40, during any thoracoplasty operation.

Statistics are hugely in favor of the two-stage operation; in Sauerbruch's earlier series there were 169 one-stage operations, with 2 operative deaths, and 21 deaths within the first three weeks, a total mortality of 13.6 per cent; there were 154 two-stage operations with 1 operative death and 5 others in the first three weeks, a total mortality of 3.9 per cent. In his later series there were 5 deaths (27 per cent) among 19 one-stage operations, and 2 deaths (4.2 per cent) among 47 two-stage operations. Stöcklin reports 9 operative deaths (28.1 per cent) among 32 one-stage cases, and 9 operative deaths (31 per cent) among 29 two-stage cases: it may be suggested that it is probable that the patients subjected to the two-stage operation were far sicker than the others, and that this may account for the fact that the figures of this series demonstrate no advantage for two stages. Jacobaeus and Key, Jessen, Ranzi, Welles and many others use two stages exclusively. It may be said in brief that there is widespread preference for the two-stage operation, but that one stage may be preferable if the patient is in excellent general condition, if the mediastinum is well fixed to prevent undue displacement of heart and trachea, and if the surgeon's technic is sure and rapid—a combination of circumstances that is met with very rarely.

Interval Between Stages. In the average case there is regeneration of rib from the remaining periosteum, often with bony bridging between ribs and with rigid fixation of the chest wall, six to eight weeks after operation. As stated above, some surgeons remove the periosteum to prevent this. If it does not occur, maximum retraction of the chest is not reached for nine months. It is clear that it is of great advantage to complete the second stage before bone regeneration occurs, because the progressive retractions of the upper and lower chest are reciprocally helpful and a rigid bulging of the one hinders maximum retraction of the other. It follows then, the patient's condition permitting, that the second stage should be done within six weeks of the first. Most surgeons give the interval as from two to three weeks; Davies says ten to fourteen days; Ochsner and H'Doubler, not more than six weeks. Sauerbruch says at

least two or three weeks. If the patient's condition has necessitated postponement of the second stage until new rib formation has occurred (Archibald recommends waiting six to twelve months if in doubt) it may be necessary, at the second operation, to remove some of this bone with chisel and mallet or with rongeurs.

Sauerbruch, Wilms, Brauer and Eloesser consider a partial large artificial pneumothorax over the less diseased lobe, followed by a partial thoracoplasty over the more diseased, adherent lobe, an absolutely ideal procedure. Tuffier and Eizaguirre prefer to use pneumolysis instead of partial thoracoplasty, in conjunction with partial pneumothorax. With either technic only one surgical operation is necessary, the diseased parts are permanently compressed, and the less diseased part of the lung resumes function when the pneumothorax is finally released. This combined pneumothorax-thoracoplasty is far safer than attempts to produce a complete pneumothorax by stretching adhesions with high intrapleural gas pressures.

Sauerbruch has now used this technic wherever possible for ten years, and has had splendid results, as has Stöcklin with 30 cases. As it is usual for the greatest disease and the most extensive pleural adhesions to be in the upper chest, artificial pneumothorax is usually induced below; this accustoms the heart and respiration to new conditions, and militates against aspiration when the partial thoracoplasty is done. Three weeks later, or when the intrapleural pressure is zero or slightly minus, ribs VII to I inclusive are resected by the paravertebral route. If the intrapleural pressure is then found to be too great it may be reduced by withdrawing gas from the pneumothorax. Great care must be taken not to wound the pleura when resecting the ribs that overlie the upper limits of the pneumothorax; if this occurs effusion and subsequently empyema are very liable to develop. In case the worse lesions were below and the pneumothorax partial above, the lower five or seven ribs would be resected.

The partial pneumothorax should be maintained for at least one year, if for no other reason than to prevent the grossly diseased part of the lung from slipping away from the compression of the overlying thoracoplasty. If the pneumothorax should be "lost" and adhesions form and compression of that part still be needed, completion of the thoracoplasty would be indicated. If both upper and lower lobes were severely diseased at the time of operation Jessen and Gravesen would prefer the permanent action of a total thoracoplasty to a combination of partial thoracoplasty and partial pneumothorax.

It happens sometimes that the Sauerbruch operations described above do not produce sufficient compression and rest to control the disease. Some supplementary operation then becomes necessary. Parts of the upper cartilages and anterior ribs (I to IV, or as many

as I to VIII) may be removed through a parasternal incision, as Wilms used to do routinely, and as Sauerbruch, Bérard and others do now. Phrenicotomy may be done, but this is more commonly performed as a preliminary to the first thoracoplasty. Pneumolysis is the supplementary operation of choice in a great majority of cases.

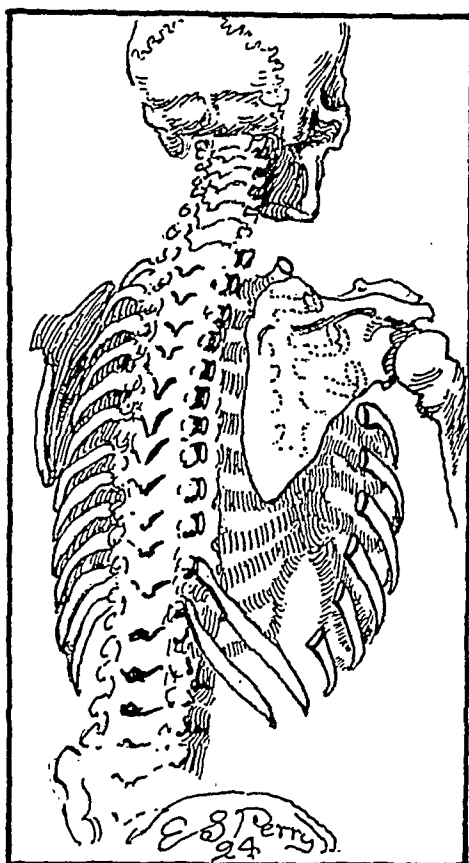


FIG. 9.—Extent of rib resection in Brauer's subscapular paravertebral thoracoplasty. The scapula falls against the upper lung and aids in compressing it.

X. Brauer's Subscapular Extrapleural Paravertebral Thoracoplasty
This operation differs in no way from the typical Sauerbruch operation, except that it resects greater lengths of ribs from beneath the scapula, allowing it to fall in on the lung and exert maximum pressure over the seat of maximum disease. Brauer has used this technic since 1911, and is greatly pleased with his results. It is his belief that in severe disease the results are directly proportional to the amount of lung compression, and that in many cases the compression obtained by the Wilms and Sauerbruch operations is insufficient. Stöcklin and Schreiber, Bull, Lorey, Jacobaeus and Key incline toward the Brauer technic.

Brauer does not remove the XI rib, nor the I if the apex has retracted below it. His average resections are: X, 10 to 13 cm.;

IX, 12 to 16 cm.; VIII to V, 15 cm.; IV, 13.5 cm.; III, 12.8 cm.; II, 8.8 cm.; I, 3.5 cm.; total 125 cm. To facilitate removal of the ribs lying under the axillary border of the scapula he sometimes makes a supplementary incision in the axilla. He aims to have the posterior cut rib-ends exactly even with one another. His plates show an even greater lung compression than obtained by the old Brauer-Friedrich operation. The shoulder does not descend much, movement of the arm is not impaired, there is little gross visible deformity, and yet there is maximum compression. The dangerous chest-wall flutter of the Brauer-Friedrich operation does not occur as ribs remain in the inferior anterolateral area of the chest which is but poorly protected by muscles against flutter.

Theoretical objection to the Brauer operation might be offered on the grounds that the arm and shoulder movements would tend to tug at and irritate the lung upon which the scapula rested, and to which it was adherent, and that this would tend to activate the tuberculous lesions. Adams has reported a case of chronic, non-tuberculous empyema cavity in which a somewhat similar operation was used with the result that the arm movements, transmitted to the lung by way of the scapula, caused the collapsed lung to expand. However, Brauer's reported results are unsurpassed.

XI. Extrapleural Pneumolysis. Pneumolysis is the separation of a lung or a part of a lung, together with both its visceral and parietal pleuræ, from the ribs and chest wall. It effects relaxation or compression of the lung. The space created by the separation may be filled with various tissue grafts or tampons, or not filled at all. Pneumolysis is used as an independent procedure, or as concomitant with, or as supplementary to, a thoracoplasty. It is rarely used except for the upper lobe, and when limited to the apex is commonly termed "apicolysis." As it is only practical to separate the lung to a limited extent, it follows that the procedure is indicated only to compress circumscribed lesions—cavities and lesions especially at the very apex, which is relatively less compressible by the usual thoracoplasty than the rest of the lung. It may be able to control persistent hemorrhage.

Pneumolysis Concomitant with Thoracoplasty. As precaution against insufficient compression by thoracoplasty Bull, Shivers, Archibald, Stöcklin and Schreiber routinely perform apicolysis immediately after resecting the upper ribs. I believe that the mere freeing of the lung, without leaving the space thus created full of something more substantially compressing than air (unless frequently renewed) does not warrant the time consumed and the danger of tearing into infected pleural or lung tissue. The additional lung compression is lost as soon as the extrapleural space obliterates itself by absorption of its contained air.

Pneumolysis secondary to thoracoplasty is a very valuable procedure for cases whose lesions, usually stiff-walled cavities, have

not been sufficiently compressed by a thoracoplasty. As improvement and fibrous encapsulation may continue for from six to twelve months after thoracoplasty, at least six months should have elapsed before pneumolysis is advised. Incision for this supplementary operation may be made either anteriorly or laterally, but in many cases it is preferable to open the upper end of the former paravertebral incision, resect sections of the upper three or four ribs, if regeneration has occurred, and proceed to separate the lung from behind (Sauerbruch; Ranzi).

Pneumolysis as an Independent Procedure. This has the advantages and many disadvantages of all partial procedures, which have been discussed above under "choice of operation" (page 279). It has certain specific disadvantages that must be mentioned: (1) The danger of tearing into infected pleura or lung at operation is a real one; (2) "fills" or grafts used to fill the space created between lung and chest wall not infrequently cause infection and are extruded, sometimes through the incision, sometimes into a pulmonary cavity because of pressure necrosis of its wall (Sauerbruch saw this occur 3 times among 40 cases); (3) a large "fill" causes greater pressure upon the mediastinum than does a modern thoracoplasty, and sometimes the dyspnea and cardiac disturbance are so great as to demand removal of the "fill."

As an independent procedure Sauerbruch thinks it indicated only where very localized tuberculosis is entirely inactive, and so shrunken as to demand release of tension; it is his opinion that if active disease, even when circumscribed, demands operation at all, it demands a more effective operation than pneumolysis alone. Tuffier, the originator of the operation, still believes that it is indicated for apical disease in preference to thoracoplasty, which he considers dangerous and complicated and should be reserved for cases with very extensive disease. That pneumolysis as an independent operation has effected many cures is indisputable; but that, everything considered, it is far inferior to total, or even partial thoracoplasty is a fair deduction from the evidence.

Technic. The anterior or axillary routes are used by all except Ranzi, Henschen and Sauerbruch, who prefer paravertebral incision on the grounds that it gives best access to the costovertebral gutter which they believe contains the most important part of the lung to free and compress—unless the cavity or worse lesions are far anterior; they further hold that a posterior "fill" is less liable to embarrass the mediastinum and great vessels, and that the thick muscles of the back afford the best protection against extrusion of a "fill." For the anterior route, incision is made in the direction of the fibers of the pectoralis major, and 3 to 4 cm. of the second, or second and third, or second, third and fourth ribs removed parasternally. For the axillary route a J-shaped incision is made over ribs III and IV, and 6 to 8 cm. of each resected, and excellent

opportunity is afforded for extensive pneumolysis (Bull). By the paravertebral route a few centimeters are removed from ribs II and III.

After the rib sections are removed, the parietal pleura is carefully exposed by splitting the intercostal muscles and endothoracic fascia, or by dividing with a knife in the vertical direction, the posterior rib periosteum and endothoracic fascia, which are normally adherent. Then with some blunt instrument, or better with the index finger, perhaps covered with gauze, the lung with both pleuræ adherent to it is very carefully separated from the chest wall. Great caution is needed to prevent tearing into superficial cavities or other lung lesions; it is important that the separating finger or instrument always work against the ribs and intercostal structures, rather than against the lung; it is safer to create a broad space before advancing, rather than to work in a long, narrow channel. It may be necessary to divide certain very tough adhesions with scissors or knife; in certain cases it is impossible to effect separation at all. The firmest adhesions are liable to be found over the vertebral bodies (Tuffier). To approach too near to the mediastinum, either anteriorly or posteriorly, is to expose it to the danger of acute infection, the germs being freed from latent foci in the pleura; Henschen has advised rubbing iodoform powder into the raw surfaces to counteract this danger. The endothoracic fascia is often not well defined, and no particular care need be exercised to commence the pleural separation internal to it, as it is soon torn through if separation is begun external to it. It is not advisable to use the interpleural space as the line of cleavage, as the danger of stirring up infection and of tearing into the lung is greater than if the separation be made external to both pleuræ. Sauerbruch and Roux-Berger warn against performing pneumolysis in the presence of a partial pneumothorax because of the danger of tearing into it; if this occurs the danger of a fatal empyema is great. Jessen and Ranzi, on the other hand, recommend a somewhat limited pneumolysis, after resection of a part of a single rib, directly over an adhesion that is preventing the full efficient action of an artificial pneumothorax and that is not suited for Jacobaeus' cauterization. Jessen uses no "fill;" Ranzi uses a fat graft, or "Humanol," a liquefied human fat. Jessen determines the exact position of the attachment of the adhesion to the chest wall with the roentgen-ray; Ranzi outlines its position by puncturing the chest wall with a needle and observing its distance from, and relation to the adhesion through a thoracoscope. These operations cannot be recommended.

Hemorrhage from the separated surfaces may usually be controlled with temporary packs. Henschen has used hydrogen peroxide; theoretically it is of questionable wisdom to permit contact of gas bubbles under pressure with open pleural veins, in view of the frequency with which air-embolus is believed to occur from the

pleura. No case of so-called pleural eclampsia has been reported as due to pneumolysis. If a pulmonary cavity should be torn into during the operation it should be packed with gauze, and nothing further done. If a thin cavity wall is known to be beneath the site of operation it may be wise to pack the extrapleural space for a few days, rather than to introduce a "fill" at once. If the pack does not cause spontaneous rupture of the cavity, the "fill" may safely be placed; if the cavity does rupture it should be packed and drained until it has filled with granulations (Sauerbruch).

"*Fills.*" Many methods have been devised to fill the extrapleural space. The following have been used: fresh or preserved grafts of omentum, lipomata, subcutaneous fat, fibroids, bone fragments; pedicled grafts of pectoral muscle; inflatable rubber bags; maintained extrapleural artificial pneumothorax; lumps of paraffine; gauze tampons. Of these, fat and pectoral grafts, paraffine and gauze tampons are the only ones extensively used at present. The colpeurynter-like bags of Gwerder and Jessen and the inflated rubber glove of Kroh are objectionable because infection of the raw surfaces is unavoidable. Gas from an extrapleural pneumothorax (A. Mayer) is too rapidly absorbed to make the method practicable, and early obliteration of the cavity by adhesions creeping from its limits is inevitable. Jessen has obtained some "results" by leaving part of his incision open to form a sinus between the extrapleural cavity and the skin; as the air pressure then remains the same in the cavity and in the trachea, the lung stays collapsed. He has used this technic only when artificial pneumothorax or thoracoplasty was impossible, or when he has created such a large extrapleural cavity that it was impracticable to fill it with grafts or paraffine. Four patients treated by Jessen in this manner died of aspiration pneumonia; he does not report the total number of operations.

Gauze Tampon "Fill" of Schlange and Sauerbruch. In 1907 Schlange filled a pneumolysis cavity with iodoform gauze for hemoptysis. Sauerbruch prefers the tampon "fill" to all others; he packs snugly for six to eight weeks, and then permits the remaining pocket to become filled with granulations, which obliterate it. If after separation of the pleuræ from the chest wall he thinks the pleuræ are too thick to "give" under moderate tampon pressure, he pares away some of their thickness, and then packs. Roux-Berger changes the gauze pack every five days. Jessen tampons tight for fourteen days, and then secondarily sutures the wound. Stöcklin much prefers a paraffine "fill" to temporary tamponade as he believes that the latter technic the granulations which obliterate the hole change to scar and must eventually stretch the lesions that had been compressed by the pressure of the tampon, and also pull open cavities whose walls may have been approximated.

Fat "Fill" of Tuffier. Tuffier was the first to perform pneumolysis (1891). In 1910 he "filled" with a piece of fresh human omentum, removed during another operation. In 1911 he used a fresh lipoma. He claims that these grafts become firm fibro-adipose tissue. Baer says that fat grafts become absorbed too fast for the lasting compression demanded for tuberculous lesions. Archibald says they are absorbed, or changed into fibrous tissue. Sometimes sterile effusions will form about these grafts, and, unless aspirated promptly, cause their extrusion. Tuffier is still using fat "fills," and since the War has had no accident or elimination. He no longer uses the Baer paraffine "fills" because he believes they are less well tolerated than living grafts, and because they are so frequently eliminated.

Bull has used fat grafts 12 times, but does not report his results. He now uses abdominal wall fat, together with the superficial fascia, in preference to fat from the thigh, as it is less stiff, and so molds itself better to the irregularities of the cavity. Morrison and Eliasberg also use fat grafts.

In 1914 Tuffier reported 10 clinical successes out of 15 cases; 4 grafts were eliminated; 2 patients died several months later from progression of disease on the originally better side. Jessen reported 6 improvements out of 6 cases, but five years later 4 of them were dead and 1 of the 2 living had a permanent sinus. Kalb reported 2 successes and 1 failure; Oeri, 3 successes; Ulrici, 1 improvement; Rieckenberg, 2 very good results; Wilms, 5 cases without any elimination. It should be mentioned that in these cases pneumolysis was used as an independent procedure (without thoracoplasty), and that the poor results may be explained upon the grounds that poor results are to be expected from any partial procedure.

Paraffine "Fill" of Baer (1913). Five or 10 gm. lumps of a mixture of paraffine with a melting point of 48 to 56° C., 0.5 per cent bismuth carbonate, 0.5 per cent iodoform are packed into the cavity with spatulae and various sized spoons.* Jessen uses a mixture of wax and vaseline as it is lighter than Baer's mixture and is more slowly taken up by the tissues. Davies has recommended pouring in liquid paraffine, but Sauerbruch warns against this as it devitalizes the tissues.

There are two principal objections to the method: (1) Large, heavy masses may cause threatening mediastinal pressure symptoms requiring removal of the "fill." One case of Sauerbruch's developed cyanosis and orthopnea, and the "fill" needed to be removed and the extrapleural space lightly tamponed. Two other of his cases, having 1000 gm. and 1200 gm. "fills," developed some untoward symptoms, but not severe enough to demand removal of the "fills." Henschen,

* Further detail as to the technic of the operation may be found in a recent article by Baer: *Plombierung bei Lungentuberkulose*, München. med. Wehnschr., 1921, 68, 1582.

on the other hand, once used 1800 gm. and made no mention of complications. (2) Paraffine "fills" are essentially foreign bodies in the tissue and as such are liable to be eliminated, whether infected or not. This occurred in 7 of Sauerbruch's 28 cases, but in none of Stöcklin and Schreiber's 13. C. Spengler lost 2 large "fills" (800 gm. and 1000 gm.), one rupturing into a pulmonary cavity, the other externally. Rivière and Romanis managed to retain one that threatened elimination by repeatedly aspirating the sterile effusion that bathed it; another of their "fills" was lost because another physician incised into the effusion instead of aspirating it. It has been learned that repeated aspirations of the sterile effusions which many paraffine "fills" excite will prevent elimination in a large majority of cases, provided aspiration is commenced as soon as fluid is demonstrable.

Good results with Baer's paraffine "fills" have been reported by Baer, Eiselsberg, S. Neumann, Kalb and Oeri. In 1921 Baer reported 4 cases of bilateral disease with cavity, greatly improved five to eight years after pneumolysis and paraffine "fill" on the worse side, and 2 other cases of unilateral disease greatly improved two and a half and three years after operation.

Ranzi has reported 10 Baer "fills" and 1 fat-muscle "fill" after pneumolysis. The fat-muscle case died on the twentieth post-operative day of mediastinitis consequent upon a tear into a pulmonary cavity. There were 4 other deaths (1 in ten months following rupture of the paraffine into a bronchus; 2 of tuberculosis; 1 of cause not given); 2 were worse at two years; 1 was improved at two years, and 3 much better, one and a quarter to two and a half years. The largest paraffine mass used weighed 350 gm. Kutscha-Lissberg used the Baer technic in 6 cases. Three died in from seven months to two years; 2 were greatly improved, and 1 was cured. He is now of the opinion that two of the patients who died, both with lesions of the apex and beyond, should have had total thoracoplasty. However, most of these and Ranzi's patients had involvement of only a part of one lobe, and it is almost indisputable that a total thoracoplasty would have furnished far better results than these.

Muscle "Fill" of Archibald. An oblique incision is made from about the midsternum to the deltoid, and most of the sternal and costal fibers of the pectoralis major, and if desired all of the pectoralis minor, are detached; this fashions a large graft with a pedicle at the acromiothoracic axis; or a pedicle may be left at the sternum. About 6 cm. of ribs II, III and IV are now resected parasternally, and pneumolysis performed; access may be difficult to the posterior inferior surface of the upper lobe. The muscle graft is now stuffed into the hole and tacked with a few catgut stitches to the periosteum. This method is a valuable one when used as supplementary to a primary thoracoplasty. The graft is almost certain to live, and the

function of the arm is but little impaired. It has the disadvantage of not offering a large enough "fill" where a relatively large extrapleural space has been created, or where the pectoral muscles are small in a thin subject. As minor modifications of this procedure I suggest: (1) An S-shaped incision in preference to a straight incision, or to the more complicated rectangular flap; this incision enables the surgeon easily to disinsert the lower fibers of the pectoralis major and affords better exposure of its upper-inner fibers; (2) inclusion of the superficial fascia and part of the subcutaneous fat in one piece with the pectoral graft in those cases where the surgeon expects to create a larger extrapleural hole than the usual pectoral graft could fill; (3) section of the internal and external anterior thoracic nerves as they enter the under surface of the pectorals. On theoretical grounds it is preferable that muscle adherent to a tuberculous lung be paralyzed rather than subject to active contractions; a possible objection to this suggestion is that the graft would lose volume owing to muscle atrophy.

Archibald and Shivers have occasionally pulled the graft backward over the separated apex and stitched it to the cut vertebral muscles of the scapula—this being done at the same time as the upper stage of a paravertebral thoracoplasty. This complicated and time-consuming technic hardly justifies the advantages gained.

Bull has recently been using Archibald's pectoral graft. Wilms has used free muscle grafts, but found that they became almost entirely transformed into connective tissue, and lost volume; he found, however, that this connective tissue made an excellent bed for a subsequent paraffine graft.

XII. Open Intrapleural Pneumolysis. When adhesions prevent a satisfactory pulmonary compression with artificial pneumothorax, some surgeons open the chest and divide the adhesions with the fingers or with a knife. They claim that this is less dangerous than attempting to stretch or rupture them with high pneumothorax pressure, and that as it is non-deforming, it is preferable to even partial thoracoplasty. If the adhesions are in the upper chest it is usually necessary to resect one rib in order to obtain satisfactory exposure with thoracotomy. Adhesions are divided close to the ribs if sharp dissection is used, thereby attempting to avoid lung tissue or cavities which may be component parts of the bases of some adhesions. Bleeding vessels may be directly ligated or closed with a cautery.

Bertier, Rist and Lecène report a favorable result, that is, a previously insufficient pneumothorax compression was made sufficient. Bertier and Delage report a failure. Schottmüller and Gravesen reports very favorable results from manual separation of the adhesions; Rivière and Romanis a satisfactory separation, but the later development of a thoracic sinus. Eden reports the rupture of a superficial cavity to the pleura several days after operation. Sauerbruch

in 1920 reported 5 cases in which he made a small incision in the chest wall and severed the adhesions with a thermocautery: 1 did well; 1 did well for three months and then the formation of a purulent exudate demanded an extrapleural thoracoplasty which was successful; 1 died in two days; 1 in three weeks, and 1 died after a thoracoplasty which the condition demanded: in the last 2 cases he attempted to separate adhesions from over the entire upper lobe.

The reported results clearly indicate that open intrapleural pneumolysis is a dangerous procedure; the results of partial thoracoplasty or partial extrapleural pneumolysis, or phrenicotomy combined with partial pneumothorax are far superior.

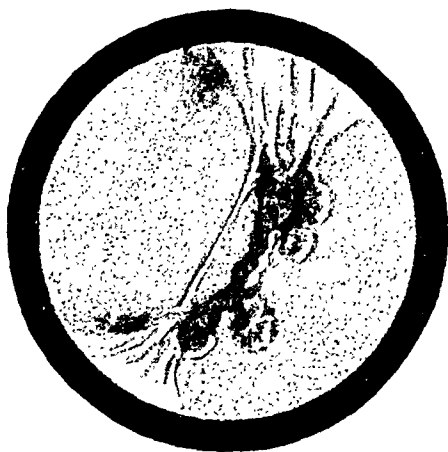


FIG. 10.—Two cord-like adhesions stretching across a partial artificial pneumothorax, as seen through a thoracoscope. The heavier one has been partly burned through with an electrical cautery. (After Unverricht.)

XIII. Closed Intrapleural Pneumolysis. Jacobaeus has devised a method of dividing adhesions without the need of open thoracotomy. He introduces two cannulae under local anesthesia, near where the roentgen-ray shows adhesions that are preventing sufficient compression with artificial pneumothorax; into one he introduces his "thoracoscope," which is similar to a cystoscope, and which enables him to see the adhesions to be severed; into the other he inserts a thermocautery which burns through the adhesions.* He has completed this operation successfully in 55 (73 per cent) of 75 cases; Gravesen in 22 (63 per cent) of 35 cases; Unverricht completely cauterized 4, and incompletely cauterized 4 of 10 cases; Jacobaeus and five other physicians successfully cauterized 85 (70 per cent) of 121 cases.

This procedure is open to many objections. When completely successful it merely prepares the patient to receive a total artificial pneumothorax. In Jacobaeus' hands there has been a mortality

* The necessary instruments, including a tissue specimen remover, as designed by Unverricht, may be purchased from Georg Wolf, Karlstr. 18, Berlin.

of 6 per cent. He considers conveniently located adhesions up to "little finger size" suitable for cauterization. Holmboe has seen it followed by hemorrhage, pyopneumothorax and thoracic sinus; several times he saw signs of shock. He examines all of his pneumothorax patients with the thoracoscope. Of the 27 in his published series 9 needed the cautery; of these 9 the artificial pneumothorax made possible by the operation was successful in 5, partially successful in 2, and unsuccessful in 2. An attempt of his to burn through a too thick ("thumb-sized") adhesion resulted in virulent empyema and death.

Cauterization is frequently followed by effusion which may become purulent and secondarily infected. A patient of Jessen's died of a purulent exudate and progression of the tuberculosis. Seven of Jacobaeus' 75 cases, 6 of Gravesen's 35, and 5 of Unverricht's 10 were complicated by tuberculous empyema, some of them fatal. Jacobaeus believes it usually possible to distinguish a prolongation of a pulmonary cavity into an adhesion by its bluish color and by the fact that it bulges when the patient coughs, and so to avoid it. Lung tissue or prolongation of a cavity capable, if opened, of infecting the pleura, may extend 1.5 cm. into any adhesion of diameter greater than 1 cm. If bleeding occurs from the severed end of an adhesion usually it may be controlled with low heat in the cautery, or with the special forceps devised for the purpose by Holmboe, or by injecting sufficiently large quantities of normal saline solution into the pleural cavity (Jacobaeus). Among the 200 reported cases of adhesion cauterization, there have been 7 hemorrhages from the severed adhesions, and 1 of these was fatal.

The smoke generated by the cautery may so cloud the field of vision that further cauterization must be postponed, or attempts made to aspirate the smoke-laden air. Sudden movements of the patient may cause the cautery to enter the lung. If it sticks it must be jerked loose, and this is very painful. Only certain narrow, fairly long adhesions are suitable for division by cautery; after the thoracoscope has already been introduced it may be discovered that the adhesions are not suitable for the operation.

Sauerbruch's opinion, concurred in by Moreau and Olbrechts, is that the dangers and uncertainties of the method do not justify its use simply to make possible a more satisfactory artificial pneumothorax; he has never used it, and would always prefer partial thoracoplasty or extrapleural pneumolysis combined with partial pneumothorax. I believe it will prove a valuable addition to artificial pneumothorax therapy if its use is strictly confined to those patients whose restricting adhesions do not number more than two or three, and are at least 3 cm. in length and not more than 0.75 cm. thick, and which can be burned through in one short operative sitting.

PARALYSIS OF DIAPHRAGM. In 1911 Stuertz proposed phrenicotomy for progressive lower lobe tuberculous lesions, especially for

cavity. Since then its indications have been widely extended, and modifications of technic introduced; in Sauerbruch's Clinic alone it has been used several hundred times for many kinds of disease.

The phrenic nerve takes origin from cervical roots III, IV and V. Its main stem runs inferiorly and internally, obliquely across the scalenus anticus muscle and beneath the subclavian vein to the diaphragm. From the inferior cervical sympathetic ganglion and from the suprapleural plexus it receives some sympathetic fibers. Twenty or 30 per cent of all persons have an accessory phrenic, which usually arises from the fifth cervical root and runs together with the nerve to the subclavius, or separately, in front of the subclavian vein to join the main phrenic stem 4 to 5 cm. from the first rib, just centrad to the pulmonary hilus. Very rarely an accessory phrenic may arise from some other root than the fifth cervical, and descend separately or with the *ansa hypoglossi*. The periphery of the diaphragm also receives sensory nerve fibers from the lower six intercostal nerves; the twelfth nerve supplies motor innervation to the few fibers arising from the twelfth rib, but the other intercostal nerves carry no motor fibers to the diaphragm (Willy Felix).

Complete paralysis of one-half of the diaphragm by interruption of both main and accessory stems of the phrenic causes that half to rise passively into the chest and to remain at rest, except that its central tendon may be tugged at slightly, almost negligibly, by the normal movements of its other half, or that it may move slightly, in a paradoxical sense, with the respiratory changes of pressure of its pleural cavity (Kienbock's phenomenon). The diaphragm atrophies and becomes a parchment-like membrane; unless hindered by many pleural adhesions, or an unusually stiff infiltrated lung, it may be expected to continue to mount into the chest cavity for some months after operation. Clinically a certain amount of pulmonary rest and compression are produced, especially of the lower lobe, and if there are no pleural adhesions the upper lobes are similarly affected. It is more exact to speak of a relaxation of the lung than of a compression. Even when the tuberculous lesions are predominantly in the upper lobes it is usual for some clinical improvement to follow phrenicotomy: fever, pulse, cough and expectoration become less, and upper lobe cavities may be seen by roentgen-ray to be definitely narrowed (Zadek). Contrary to expectation, cough and expectoration are easier after paralysis of the diaphragm than before; this is explained on the grounds that a lax diaphragm allows the strong abdominal muscles, always much relied upon in coughing, to act more quickly. Phrenicotomy has not been known to cause dyspnea or other respiratory disturbance. In fact Jehn, Sauerbruch, Lehman, Dehler and Stern have performed bilateral phrenicotomy for persistent singultus, or to permit artificial respiration in diaphragmatic tetanus, and have seen no noteworthy respiratory disturbance; Jehn's patient led an active life three and a half years after the operation and was never dyspneic.

Observations upon Walter's patients who had had "simple phrenicotomy" (no attempt to resect the accessory branch when present) showed that some of the diaphragms resumed small normal, instead of paradoxical, movements within a month of operation (Goetze has seen this occur within a few days); it may be assumed that their accessory phrenics had compensated. Fritz saw small normal diaphragmatic movements in 25 per cent of simple phrenicotomies. After radical phrenicotomy (which includes resection of the accessory branch) the diaphragm never regains its tone nor loses its slight paradoxical movements; the state of functional rest is nearly absolute.

After a simple phrenicotomy the diaphragm rises to a level 3 to 7 cm. higher than normal, and higher on the right than on the left. Normally the right diaphragm is 1 to 2 cm. higher than the left; on forced inspiration there may be a difference of 2 to 4 cm. Chaoul and Stierlin state that scarcely any change in form is visible by roentgen-ray in the costophrenic sinus after phrenicotomy.

H. Alexander, reporting 14 of Sauerbruch's and Schreiber's cases, found an average rise of 2.15 cm. after simple phrenicotomy and 4.25 cm. after radical phrenicotomy. In 17 cases of simple phrenicotomy Fritz found the difference between the two halves of the diaphragm to be 2 to 4 cm. in full inspiration; in 11 cases of radical phrenicotomy the difference was 7 cm. when the right side had been paralyzed, and 4 cm. when it had been the left side. Willy Felix found the average differences in diaphragmatic height after right and left sided radical operations upon 20 patients to be 7 cm. on inspiration, 3 cm. on expiration. Sultan has seen as great a difference as 11 cm. after right radical phrenicotomy, and 9 cm. after left-sided operation. Sauerbruch gives the differences after radical phrenicotomy as follows: After right-sided operation, right diaphragm 4 cm. higher than left in expiratory position, and 8 cm. in inspiratory position; after left-sided operation, left diaphragm 2 cm. higher than right in expiration and 6 cm. higher in inspiration. Spirometer readings are reduced 30 per cent by the operation.

Ken Kure and his co-workers found that the right diaphragms of apes did not rise after phrenicotomy; their explanation is that the weight of the liver pulling the diaphragm down more than counterbalances the negative pressure in the thorax pulling it up. Shulte-Tigger says this does not occur in man, and Felix specifically states that his fluoroscopical observations of high right-sided diaphragms were made with the patients in the erect posture.

Phrenicotomy has the disadvantages and advantages of all partial operations (see partial procedures under "choice of operation"). The following are opposed to its use as an independent procedure, but advocate it warmly as supplementary for certain cases: Sauerbruch, Brauer, Denk (experience of 26 cases), Zadek (ten years' experience), L. Spengler, Walter, Baer, Shulte-Tigger, Maendl, Felix and Sultan. Only Goetze, Frisch, Fischer and H. Alexander advise it as

an independent operation in certain cases when artificial pneumothorax is not realizable. Goetze says that 50 per cent of the cases are improved and many of them cured. Sauerbruch believes that many so-called "cures" after phrenicotomy used alone are only apparent cures, and that relapses often follow.

In addition to the advantages that may be derived from any partial operation phrenicotomy, in particular, may be valuable as: (1) A test of the better lung when thoracoplasty is being considered (see the better lung under "indications and contraindications"). Sultan advises it as a preliminary to any thoracoplasty; also to help fill empyema cavities. (2) As a preliminary to a complete thoracoplasty when the lower lobe is much diseased, or when the chest is greatly contracted and the heart displaced by the pull of fibroid phthisis or pleural scars. The final total compression and repose of the lung are greater. (3) Preliminary to a partial thoracoplasty of the upper chest in cases where the lower lung is free of disease. Sauerbruch, however, does not consider phrenicotomy without partial resection of the lower ribs sufficient assurance against aspiration at the time of operation on the upper ribs. (4) To cause enough clinical improvement in desperately sick patients to permit a later thoracoplasty; the interval should be two to three months (H. Alexander). (5) In conjunction with incomplete artificial pneumothorax. Shulte-Tigger believes that this combination has a wide and valuable field. He and Frisch consider it especially indicated where there are basal adhesions, as basal lesions are usually grave enough to demand maximum and prolonged rest and compression. (6) For the pain, dyspnea and irritative cough caused by diaphragmatic adhesions in some cases of artificial pneumothorax. (7) As supplementary to every artificial pneumothorax (Baer), in order to lessen the occurrence of exudate, and to lengthen the time intervals between gas "fills," and to decrease the size of the chest against the time when a shrunken, inelastic lung is permitted to expand on release of the pneumothorax (Goetze, Zadek, Sultan and Frisch). Zadek and Sultan have used the combination in over 50 cases since 1922, and so far are hugely pleased with the results. Zadek says that there is less displacement of the mediastinum than when pneumothorax is used alone.

Sauerbruch and Zadek call attention to the newly observed fact that fewer exudates occur in cases of artificial pneumothorax when the diaphragm has been paralyzed, and that when they do occur they are smaller. Intrapleural gas is absorbed so slowly after diaphragmatic paralysis that some patients who needed "refills" every three to four weeks before phrenicotomy, need them only every ten to twelve weeks after phrenicotomy (Sauerbruch); Zadek says that phrenicotomy lengthens the intervals between "fills" from a quarter to a third; Goetze and Frisch have advised diaphragmatic paralysis when expansion of the lower lobe by the tug of new adhesions under an effusion is feared.

To release an artificial pneumothorax and permit a scarred, shrunken lung to expand in an attempt to meet the chest wall is a hazardous procedure and not rarely followed by emphysema, mediastinal displacement, dyspnea, effusion, pain, unfolding of cavities, lighting up of infirmly encapsulated foci, and reactivation of the tuberculous disease. The narrowing of the chest, caused by the mounting of the diaphragm, largely compensates for the disproportion in volume between the unchanged capacity of the hemithorax and the diminished volume of the shrunken, fibrotic lung. I believe that these many advantages will eventually lead to the use of phrenicotomy in conjunction with almost every case of artificial pneumo-

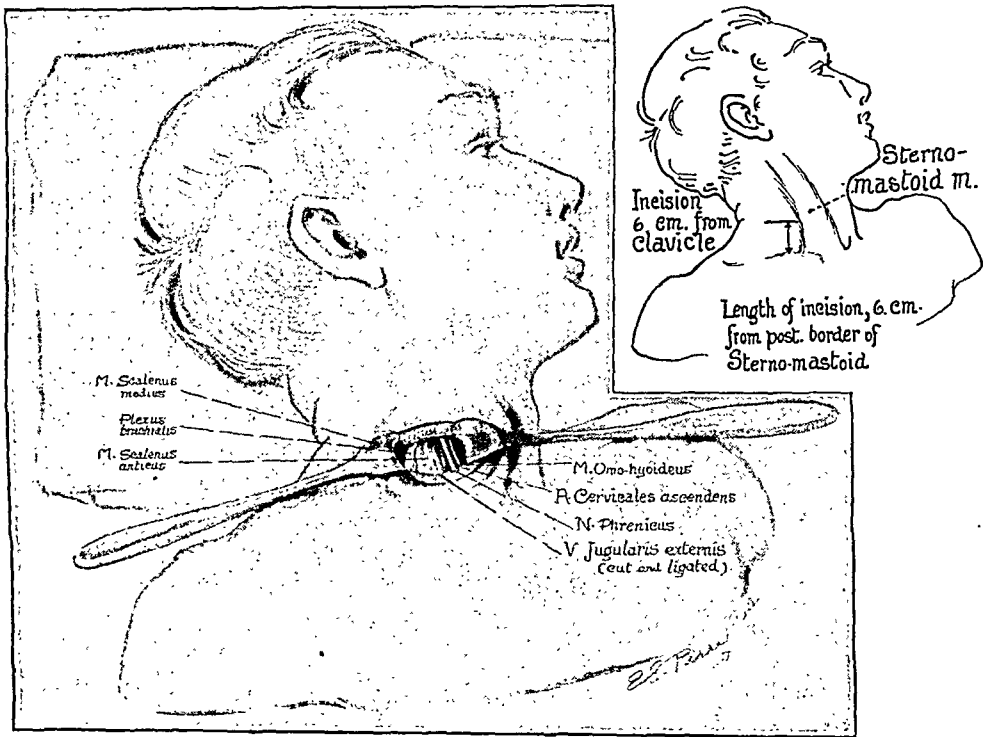


FIG. 11.—Author's incision for phrenicotomy. Surgical anatomy of the approach to the nerve.

thorax. Zadek now performs it eight to fourteen days prior to the induction of artificial pneumothorax treatment; he believes that the negative pressure within the pleura causes the diaphragm to mount higher than if paralysis did not occur until the pleural pressure were positive. Maendl finds that the positive intrapleural pressures of pneumothorax (in one case: +1, +3 cm. H_2O) do not depress the elevated, paralyzed diaphragm. Goetze performs phrenicotomy after the pneumothorax. As diaphragmatic adhesions form quite rapidly after phrenicotomy it is unwise to wait over three weeks before starting the pneumothorax. For patients with history of hemoptysis Zadek does not perform phrenicotomy until after the pneumothorax treatment has been started.

Simple phrenicotomy is strictly a minor operation. It is performed under local anesthesia in a few minutes. Commencing at the posterior border of the sternomastoid muscle 6 cm. above the clavicle, a 6 cm. transverse incision is made in the posterior triangle of the neck. The Continental surgeons use a longer incision along the posterior border of the sternomastoid muscle; it is unnecessarily disfiguring. The transverse incision leaves almost no noticeable scar. In the fatty tissue between the skin and scalenus anticus muscle some veins and branches of the transverse cervical and supra-scapular arteries may require ligation. Running across the anterior surface of the muscle, obliquely from above down and in, is the phrenic stem. Galvanic stimulation or pinching of it causes singultus and pain in the shoulder, neck, chest, heart, diaphragm and abdomen. A few drops of novocain solution should be injected into it before it is sectioned. It is preferable to resect 2 to 4 cm. of the nerve, as Kroh has found that there may be regeneration of a simply sectioned nerve within four months. Felix cites two patients whose diaphragms were functioning normally one and a half and five years, respectively, after phrenicotomy. The skin wound is closed without drainage.

Radical phrenicotomy implies resection of the accessory phrenic as well as of the main stem. This has been done only since 1921. As long ago as 1884 De Jaeger knew that simple section of the main phrenic stem did not always eliminate all diaphragmatic function. Recently Felix and Goetze have studied the anatomy of the accessory phrenic nerves, and have proposed different operative procedures to interrupt their function. Goetze considers other varieties than the branch arising with the subclavius nerve from the fifth cervical root so rare that he disregards them. After doing a simple phrenicotomy as far down as possible in order to separate from the phrenic the fibers from the inferior cervical sympathetic ganglion, he exposes the fifth cervical root through the same incision (he uses a long one parallel with the posterior border of the sternomastoid muscle), and identifies the desired branch on its (C-V root) anterior surface, and sections it. Felix performs a Thiersch exæresis of the phrenic nerve, twisting it out of the chest from beyond the place where accessory phrenics usually join it (7 cm. from the first rib, or 12 cm. from the place where the phrenic is conveniently sectioned on the scalenus anticus muscle. After giving a hypodermic of morphin. Felix employs the same incision as for simple phrenicotomy, and operates under local anesthesia; he injects 20 cc novocain solution around cervical nerve roots III to V in order to block centripetal pain impulses from the accessory phrenic. He then identifies the main phrenic stem on the scalenus anticus muscle, sections it and seizes the distal cut end with a Thiersch or hemostatic forceps, whose jaws are protected, and slowly twists the nerve until it breaks. The nerve should be carefully freed of connective tissue before it is seized, and the twists should not be faster than one in one minute.

(To be continued)

REVIEWS.

HYGIENE AND PUBLIC HEALTH. By GEORGE M. PRICE, M.D.,
Director of Joint Board of Sanitary Control and Director of
Union Health Center, New York City. Third edition. Pp. 306.
Philadelphia and New York: Lea & Febiger, 1924.

THE book is an epitome of the subject, presenting only the most salient features, and even these of necessity quite briefly. As the author says "Some subjects upon which volumes have been written are disposed of in a few lines." Considering the scope of the work, however, this has been well done. To the new third edition have been added chapters on hygiene of childhood and on food, that add considerably to the value of the work. K.

A TEXT-BOOK OF PHARMACOLOGY AND THERAPEUTICS OR THE ACTION OF DRUGS IN HEALTH AND DISEASE. By ARTHUR R. CUSHNY, M.A., M.D., LL.D., F.R.S., Professor of Materia Medica and Pharmacology in the University of Edinburgh. Eighth edition. Pp. 707; 73 illustrations. Philadelphia and New York: Lea & Febiger, 1924.

It is a pleasure to note that after a period of twenty-one years this excellent monograph has been revised and brought up to date. The chief changes are to be found in connection with cardiac therapeutics and the pharmacology of ergot, cocain, thyroid, strychnin and pituitary. A short chapter has been allotted to insulin, another to the vitamins and one to histamin action and anaphylaxis. The work as it stands will hardly find a rival in the English language as a text-book on pharmacology. A.

THE INTERNATIONAL MEDICAL ANNUAL, A YEAR BOOK OF TREATMENT AND PRACTITIONER'S INDEX. Pp. 556; 54 plates, 99 illustrations. New York: William Wood & Co., 1924.

THIS annual publication is a compendium by recognized authorities in which the recent advances in medicine and surgery are

outlined. The alphabetical arrangement according to disease is a feature of distinct advantage for ready reference. Noteworthy discussions in this issue relate to desseminated sclerosis, diabetes, asthma and the functional neuroses, by Purves-Stewart, Comrie, Wynn and Hadfield respectively

A.

DISEASES OF THE CHEST AND THE PRINCIPLES OF PHYSICAL DIAGNOSIS. By GEORGE W. NORRIS, M.D., Professor of Clinical Medicine in the University of Pennsylvania, and HENRY R. M. LANDIS, M.D., Director of the Clinical and Sociological Departments of the Henry Phipps Institute of the University of Pennsylvania, with a chapter on the Electrocardiograph in Heart Disease by EDWARD B. KRUMBHAAR, PH.D., M.D., Director of Laboratories of the Philadelphia General Hospital. Third edition. Pp. 907; 433 illustrations. Philadelphia and London: W. B. Saunders Company, 1924.

THE fact that this book since its first appearance in 1917 has been five times reprinted, including two revisions, is an ample testimony to the continued popularity of this excellent work. By its thoroughness, lucid style and pleasing make-up it has endeared itself to practitioner, teacher and student. The present third edition has been thoroughly revised and certain portions rewritten. Some of the rarer cardiac and pulmonary conditions that were omitted in previous editions are taken up, somewhat briefly to be sure, but adequate references are furnished should the reader desire to further search the literature.

K.

QUAIN'S ELEMENTS OF ANATOMY. MYOLOGY. By T. H. BRYCE, M.D., F.R.S., Professor of Anatomy in the University of Glasgow, with sections on the actions of muscles by THOMAS WALMSLEY; Professor of Anatomy, Queen's University of Belfast. Vol. IV. Eleventh edition. Pp. 310; 91 illustrations, of which 53 are colored plates. New York and London: Longmans, Green & Co., 1923.

THIS is the most recent volume in the eleventh edition of Quain, and it is interesting that its author, Professor Bryce, was also the author of the first volume of this edition, which was devoted to Embryology, and appeared in 1908. The part preceding the present was published in 1915, and the long interval which has elapsed between the two parts has been due to circumstances arising from the war. But this delay has in no way impaired the

quality of the final result. The subject is treated from a dynamic standpoint, as is proper for such a plastic system, in which so many considerations of development, phylogeny and function enter into the final product. Here is given not merely a catalogue of morphological entities, but also a functional study, which approach in places a real physiology of the muscular and fascial systems. The embryological knowledge of the author is shown in references to the development of various groups of muscles from pre-muscle tissue and muscle masses in young embryos, and their nerve connections. Seventeen pages of bibliography, mostly of the last twenty-five years, show that the scientific study of the subject is far from being a finished one. The colored plates of the various dissections will appeal to the student, while the detailed accounts of the fascia, bursæ and tendon sheaths will be referred to by the surgeon and physician.

A.

STUDIES ON SCHISTOSOMIASIS JAPONICA. By ERNEST CARROLL FAUST, PH.D., and HENRY EDMUND MELENEY, M.D., with a supplement on the molluscan hosts of the human blood fluke in China and Japan, and species liable to be confused with them, By NELSON ANNANDALE, D.Sc. *The American Journal of Hygiene*, Monograph Series No. 3, March, 1924.

THIS monograph of 339 pages is the coöperative undertaking of the Associate Professor of Parasitology and the Associate in Medicine in the Peking Union Medical College, Peking, China, and the Director of the Zoölogical Survey of India, Calcutta, India. The authors discuss the historical aspects of schistosomiasis, the morphology, biology and life history of the causative organism, its mode of migration in the body of the mammalian host, the intermediate hosts, the distribution of schistosomiasis in the Orient; the pathological anatomy, clinical manifestations and prophylactic aspects of the disease and, finally, the molluscan hosts of the human blood fluke, and the species liable to be confused with them. The work is well printed and illustrated with 36 plates and 25 test figures. The bibliography given is very complete. This excellent monograph is warmly recommended to those interested in tropical or parasitic diseases.

S.

DISLOCATIONS AND JOINT FRACTURES. By FREDERIC T. COTTON, A.M., M.D., Visiting Surgeon to the Boston City Hospital; Associate in Surgery, Harvard Medical School. Second edition. Pp. 740; 1393 illustrations. Philadelphia and London: W. B. Saunders Company, 1924.

THE reader needs no introduction to the author, nor to this the second edition of his work, for all who read on this subject must

needs have met them both at least in print. It is needless to say the book is good. The author has covered his subject most carefully and thoroughly, and in doing so has brought his own personal cases and illustrations to help elucidate the matter. He is responsible entirely for the text and for all the drawings, so that the question or the possibility of mistakes due to misinterpretation is reduced to a minimum. The book fills the wants of not only the general practitioner, but also of those who specialize in the treatment of bones and joints. It is thorough, comprehensive, lucid, nicely written, profusely illustrated and instructive. E.

OPERATIVE SURGERY. Covering the Operative Technic Involved in the Operations of General and Special Surgery. By WARREN STONE BICKHAM, M.D., F.A.C.S., former Surgeon-in-Charge of General Surgery, Manhattan State Hospital, New York, and former Visiting Surgeon to Charity and to Touro Hospitals, New Orleans. In six octavo volumes. Volume III. Pp. 1001; 1249 illustrations. Philadelphia and London: W. B. Saunders Company, 1924.

VOLUME III deals with operations upon the head, neck and thoracic wall. The special fields of the eye, ear, nose and throat are covered in a manner satisfactory for general purposes. Plastic surgery is well covered in sections upon the cheeks, lips and palate. Most surgeons, however, will not agree that it is best to wait until after the second year to repair a cleft palate. The chapter on the thyroid gland is not up to standard and a sense of proportion is violated in allotting but thirty-five pages to this subject when thirty-six pages are given to the esophagus. Throughout the book it is felt that its value would be greater if more space were given to operations of choice and less to those of occasional use or historical value. P.

OPERATIVE SURGERY. Covering the Operative Technic Involved in the Operations of General and Special Surgery. By WARREN STONE BICKHAM, M.D., F.A.C.S., former Surgeon in Charge of General Surgery, Manhattan State Hospital, New York, and former Visiting Surgeon to Charity and to Touro Hospitals, New Orleans. In six octavo volumes. Vol. IV. Pp. 842; 6378 illustrations. Philadelphia and London: W. B. Saunders Company, 1924.

VOLUME IV deals with the heart, pericardium and intrathoracic vessels, the thoracic portion of the esophagus and other intrathoracic

structures, the abdominal wall and hernia, the peritoneum and abdominal viscera. Discussion is fuller and more illuminating than in the preceding volume. The arrangement, illustration and typography are excellent as in the preceding issues and as a reference book it is unsurpassed. The reviewer does not wish to detract from these obvious merits unduly, but considering the influence which such a pretentious work will have on surgical practice in smaller clinics throughout the country he could wish that display and illustration might go hand in hand with utility. For instance, the space and illustrations given to Loreta's and Hahn's obsolete operations of pylorodiosis could have been curtailed in favor of a fuller description of Rammstedt's operation. Polya's method and Balfour's modification of gastric resection are certainly more useful than Kocher's, but receive less attention and no credit. Fig. 3529, which purports to show how to avoid vicious circle in gastroenterostomy by depicting the isoperistaltic manner of placing the jejunal loop as the proper method and the non-isoperistaltic method as dangerous, overlooks the fact that the latter is the operation employed by the Mayo Clinic and, under their influence, by the greater number of surgeons in this country, and has nothing to do with vicious circle. In spite of these comments which are offered as suggestions rather than strictures the book is commended as a valuable addition to the surgeon's library. P.

PATHOLOGICAL TECHNIC. A Practical Manual for Workers in Pathological Histology and Bacteriology, Including Directions for the Performance of Autopsies and for Clinical Diagnosis by Laboratory Methods. By FRANK B. MALLORY, M.D., Pathologist to the Boston City Hospital; and JAMES B. WRIGHT, M.D., Pathologist to the Massachusetts General Hospital and Assistant Professor of Pathology, Harvard Medical School. Eighth edition, revised and enlarged. Pp. 180; numerous illustrations. Philadelphia and London: W. B. Saunders Company, 1924.

A NEW edition of this well-known work, the best of its kind in the English language, is always welcomed by pathologists. In the present case it is doubly welcome after a lapse of six years, since the previous edition, instead of the usual three years. More than one hundred pages have been added, chiefly in the chapters on histology, on the nervous system (by S. T. Orton) and on the blood, the last (contributed by Dr. Buckman) now including sections on hemoglobin, coagulation, volume, resistance, reticulocytes and so forth. There is a small section on medical photography, which if it helps in obtaining results in any way comparable to those of Dr. Mallory will be indeed welcome. The omission of the small section

on methods of examination of tissues and fluids is to be regretted, but this is more than compensated for by the valuable new inclusions. K.

RADIUM REPORT OF THE MEMORIAL HOSPITAL, NEW YORK. Second series, 1923. Pp. 305; 55 illustrations. New York: Paul Hoeber, 1924.

THIS report consists of articles by the various members of the staff of the Memorial Hospital. In the seven years intervening between the publication of the first report and this one the radium therapy of malignant tumors has made great strides forward, and in this advance the Memorial Hospital has been the pacemaker in this country. For this reason their careful conservative conclusions on selection of cases, the technic of therapy and the results of treatment can be accepted as the best available in the field. The book is primarily of interest to radium therapists, yet the internist can form from it opinions based on the widest of clinical experience as to what tumors are best suitable for radium therapy, and what results are to be expected. L.

THEORIES OF MEMORY. By BEATRICE EDGELL, M.A., PH.D., University Reader in Psychology, Medford College, University of London. Pp. 174. New York: American Branch, Oxford University Press, 1924.

THE author reviews some of the theories of memory that have been advanced in the past, in particular the biological doctrine of behaviorism and the memory conceptions advanced by Bergson, Russell, Alexander and Holt. Criticisms and objections are raised, and an attempt to answer them made in a discussion of memory as a purely psychological conception. The work is of interest to physiologists and psychologists alike, but because of its highly technical character has only a limited appeal. K.

THE CULTURE OF THE ABDOMEN. By F. A. HORNIBROOK. Pp. 67; 26 illustrations. New York: William Wood & Co., 1924.

THIS is a very excellent book by an author who seems to have had a large amount of experience in the treatment of the disorder he wishes to remedy. Like most faddists, he attributes entirely too much to obesity and chronic constipation, but, as with most enthusiasts, he probably feels that this is necessary in order to impress the

reader with the validity of his contention. There is no doubt that a great deal of what he has to say is true and, what is more important, that excellent results are shown by the methods of treatment which he details for the strengthening of the abdominal muscles and improving intestinal peristalsis. M.

COLLECTED PAPERS OF THE MAYO CLINIC AND THE MAYO FOUNDATION. Pp. 1377; 410 illustrations. Philadelphia: W. B. Saunders Company, 1924.

THE fifteenth volume of the collected papers of the Mayo Clinic and the Mayo Foundation presents a decided change over the previous volume. The reviewer in the past has pointed out that the inclusion of so many papers as appeared in previous volumes has made a tome which had become unwieldy and too large for practical purposes. The editors of the new volume have also concluded that such is the case, so the present volume, although it represents a collection of every paper that is published during the year from the Mayo Clinic and the Mayo Foundation, has been reduced about half in the number of pages of contents by careful editorial supervision and by abstracting the articles that are largely technical or of interest limited to specialists. The reviewer feels that this is a decided improvement. The contents of the volume are most catholic in their quality. There are articles on almost every type of disease and disease of practically every organ in the body as well as a large number of articles more or less of a general character. M.

THE RELATIVE POSITION OF REST OF THE EYES AND THE PROLONGED OCCLUSION TEST. By F. W. MARLOW, Professor of Ophthalmology, Syracuse University. Pp. 94; 27 tables and charts. Philadelphia: F. A. Davis Company, 1924.

IN this essay the author discusses the inadequacy of the ordinary muscle balance tests in determining the absolute amount of heterophoria, and describes the technic and value of the prolonged occlusion test for bringing out the full muscle error. In applying this test he uses a ground-glass, a piece of black paper pasted on the back of one glass, or, better, a patch over one eye. The faulty eye is always occluded, and the average duration of occlusion is seven days.

By this method the author elicits the latent heterophoria, which may not have been apparent or only to a slight degree with the rapid test. Exophoria and left hypophoria are present in the

majority of cases. Heterophoria by this test has no relation to age, but may run in families. The only practical objection to the use of the prolonged occlusion test in routine practice is the number of days required to complete it. S.

PALEOPATHOLOGY: AN INTRODUCTION TO THE STUDY OF ANCIENT EVIDENCES OF DISEASE. By ROY L. MOODIE, Associate Professor of Anatomy in the University of Illinois. Pp. 567; 49 figures and 117 plates. Urbana, Ill.: University of Illinois Press, 1923.

THIS comprehensive and scholarly volume is a prominent milestone in this most recent branch of the science of pathology. The book is dedicated to Sir Marc Armand Ruffer, who coined the term Paleopathology, and whose work "on the pathology of ancient mummies forms the groundwork" of the science today. Ruffer's collected studies, published by the University of Chicago Press in 1921, under Moodie's editorship, is the first book of consequence on this subject in English. The second, the book now under view, extends the ground to be covered from the Proterozoic period, 100,000,000 or more years ago, to the beginning of the historical period. Most of the evidence naturally comes from fossil invertebrates and reptiles and other early vertebrates and is necessarily confined almost entirely to shell or bony lesions. Such compelling subjects, therefore, as the causes of extinction of races, have still to be left to conjecture: The bony lesions observed are for the most part compatible with life and many probable causes would obviously have left no trace. Such speculations are legitimately indulged in by the author (Cp. "The possibility of a widespread epidemic of the *nagana* among the ungulates of the early Tertiary, a million or more years ago"), in a manner calculated to hold the interest of the reader and stimulate further studies, without building ladders of sand. The last four chapters on the pathology of the early human races (Stone ages, Egyptians, Pre-Columbian Indians and Peruvians) will perhaps especially interest the average medical man. Prehistoric trephining with stone implements (still continued by the North African Kabyles, in Tahiti, Bolivia and elsewhere) and other primitive surgical methods have received considerable attention; but it will probably be an interesting surprise to most readers to learn that appendicitis, arteriosclerosis, hydrocephalus, poliomyelitis, prolapsus recti, psoas abscess, rickets and many other disorders have been observed in corpses from four to ten thousand years old. K.

PROGRESS OF MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND
ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES
IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SUR-
GEON TO THE PHILADELPHIA GENERAL AND
NORTHEASTERN HOSPITALS.

Eventration of the Diaphragm.—WALTON (*Am. Jour. Roentgenol.*, 1924, 2, 420) says that the term eventration represents a condition in which one dome of the diaphragm is stretched out and elevated high into the thoracic cavity, so that the abdominal viscera immediately beneath are contained within the thorax. In diaphragmatic hernia the abdominal viscera are displaced into the thoracic cavity through a normal or pathological orifice in the diaphragm. Eventration does not necessarily produce symptoms. When these do occur they are usually referred to the cardiopulmonary or digestive organs. It is found four times more frequently in men than in women. The theory of congenital origin is substantiated by the fact that it has been found in a number of infants and is usually associated with other congenital defects. It nearly always involves the left side of the diaphragm, the top of the dome, often reaching as high as the second or third interspace, anteriorly. The viscera in ectopia are usually the stomach, colon, small intestines, liver, spleen and kidney. Only 6 cases of eventration of the right side have been reported. Case reports and roentgen-ray pictures are appended to the article.

Goiter.—McCARRISON (*Brit. Med. Jour.*, 1924, 1, 989) states that there are two main factors on which the prevention and cure of goiter depend, namely: The general hygiene of the individual, especially of the intestinal tract, and the amount of iodine available for the needs of the thyroid gland and the organism generally. It is not always necessary that the water supply should be bacteriologically impure in order that the bacterial conditions in the intestines favorable to the production of goiter shall be set up. Constipation and imperfect drainage of the bowel may be equally effective in producing them, with

the hygiene at high mark; the method of prevention of goiter by iodine is at once simple, rational and cheap, and no ill consequences have been observed when it is applied in the proper way and at the proper time.

Further Observations of the Kahn Reaction in the Serological Diagnosis of Syphilis.—KEIM (*Am. Jour. Syphilis*, 1924, 8, 323) reports that preliminary studies showed that the clinical application of the test compares favorably in sensitiveness with the standard Wassermann reaction. The advantage of this precipitation test over the complement-fixation test are simplicity of procedure, rapidly of reading, reduction of sources of error, through the elimination of the hemolytic system. The clinical application of the Kahn test has been studied in 1000 cases. Two-thirds of this series were carried out by Kahn's latest procedure, in which three different serum-antigen proportions are employed and the tests are completed a few minutes after mixing serum with antigen. The results obtained indicate that the newer procedure possesses a higher degree of sensitiveness.

Clinical Observations on the Etiology of Gall Stones in Women.—SCHROYER (*Surg., Gynec. and Obst.*, 1924, 38, 344) says that cholecystitis of middle adult life in women in a large number of cases traces its origin to the first pregnancy, and as such it must be recognized as a distinct clinical entity. If this conclusion is supported by observations of other clinicians it may tend to destroy the clinical superstition that young women do not have gall stones. It may train medical men to link vague abdominal phenomena occurring during the first pregnancy and recurring during the subsequent pregnancies with the clinical finality of the gall-stone picture present in patients between the ages of thirty-five and forty-five years.

Operative Treatment of Congenital Dislocation.—DICKSON (*Jour. Bone and Joint Surg.*, 1924, 6, 262) states that absolute failure occurred in 1 of 5 cases. This failure was due to infection and not the operation. Admitting that infection is probably a certain cause of failure, it does not seem that the possibility of its occurrence is a contraindication to operative interference in these cases. The benefit which the 4 successful cases secured was due more to stabilizing the hip-joint than to the increase in length secured. The only limitation of motion which has occurred has been inability to acutely flex the hip, and this is comparatively unimportant, as it is a movement which is only occasionally used.

The Etiology and Treatment of Non-tuberculous Pulmonary Abscess.—WHITEMORE (*Surg., Gynec. and Obst.*, 1924, 38, 461) says that it is important for the surgeon performing the operations on the upper respiratory tract under general anesthesia to bear in mind the danger of lung infections and arrange his technic so as to avoid this complication. From 10 to 30 per cent of the cases may be expected to be cured by expectant treatment. Artificial pneumothorax may cure a very small number of cases. It should be used only in those cases in which the lung and costal pleura are not adherent. It is an excellent means of determining whether or not adhesions are present. Bronchoscopy

may cure a very limited number of cases if treatment is established early. Surgery offers an excellent chance for cure in those cases in which other methods of treatment have failed or are unsuitable.

Epididymotomy for Acute Epididymitis as an Office Procedure.—DORSEY (*Am. Jour. Surg.*, 1924, 38, 4) says that epididymitis is practically always secondary to inflammation of the deep urethra in the region of the ejaculating ducts. The urethral inflammation is usually associated with involvement of the seminal vesicles and prostate gland. The severity of the epididymal inflammation bears no relationship to the degree of involvement in the deep urethra. Epididymotomy invariably affords immediate and permanent relief from pain. There are no recurrences after operation, unless there is a fresh infection. The course of epididymitis is without question shortened, as is also the urethritis. Patients are probably less likely to be sterile. Treatment of the urethritis can be begun much earlier. Finally the operation can be safely and successfully performed in the office under local anesthesia.

Testicular Grafts.—WALKER (*Lancet*, 1924, 206, 319) reports that the results obtained from the treatment of testicular deficiency by means of grafts are distinctly promising. The method, however, has its limitations, for in very few of the cases that present themselves for treatment with signs of testicular deficiency is the deficiency entirely confined to the testicle. A question of greatest importance is that of the durability of grafts. The author and other authorities believe that a heterograft undergoes processes of absorption from the very beginning. Morris made the interesting observation that in 1 of his cases possessing testicles, although atrophied ones, the insertion of a graft stimulated the growth of the patient's own testes. A somewhat similar action may possibly be exerted on other endocrine tissue and the impetus given by the graft thus outlasts its life.

Dependent Drainage of the Perivesical Region.—CHUTE (*Jour. Urol.*, 1924, 11, 365) describes a simple method of dependent drainage with appended case reports. Such drainage is especially indicated in suppurations that involve the loose perivesical tissue. The most typical of these conditions is suppurative pericystitis. This type of drainage, may, however, be used to advantage in various operations that involve the probable infection of the perivesical tissues deep in the pelvis near the base of the bladder. Dependent drainage carried out in this manner is much more efficient than any type of uphill drainage that we can devise. This drainage is easily carried out. The tissues involved are not important. The time consumed is very short.

The Etiology and Treatment of Non-tuberculous Pulmonary Abscess.—WHITTEMORE (*Surg. Gynec. and Obst.*, 1924, 37, 461) says that the etiology in his own last 100 cases could be established definitely in all but 8 cases. In 66 cases there had been an operation on the upper respiratory tract under general anesthesia directly preceding the lung infection. In 48 cases tonsils had been removed, in 12 patients teeth extracted, in 2 cases septic sinuses drained, in 1 adenoids removed, in 1 a deviated septum straightened, in 1 a broken nose operated upon and

in 1 a tracheotomy was done. Pneumonia was the cause of the abscess in 22 cases. Bronchopneumonia occurred 20 times. Septic infarction was the etiological factor in 3 instances, and a bronchial esophageal fistula in 1. It is important for the surgeon performing operations in the upper respiratory tract, under general anesthesia to bear in mind the danger of lung infection, and arrange his technic so as to avoid this complication. From 10 to 30 per cent of the cases may be expected to be cured by expectant treatment. Artificial pneumothorax may cure a very small number of cases. It should be used only in those cases in which the lung and costal pleura are not adherent. It is an excellent means of determining whether or not adhesions are present. Bronchoscopy may cure a very limited number of cases if treatment is established early. Surgery offers an excellent chance for cure in those cases in which other methods of treatment have failed or are unsuitable.

THERAPEUTICS

UNDER THE CHARGE OF
SAMUEL W. LAMBERT, M.D.,
NEW YORK.

The Antiallergic Treatment of Bronchial Asthma.—Recognizing the importance of specific agents which, either by ingestion or inhalation, may cause bronchial asthma and emphasizing the necessity of testing all patients who have this condition, by means of skin tests, VAN LEEUWEN (*Therap. d. Gegenw.*, 1924, 3, 97) states, from the study of 300 cases of bronchial asthma in Holland, that from 80 to 90 per cent of the cases were sensitive to some "miasma" which was peculiar to the climate in which they lived. Two of these "miasma" which are known are found in grain infected with a mite and in grain infected with a fungus, and animal experiments have shown that it is neither the mite nor the mold but some toxic substance which gives rise to the asthmatic attacks. Patients who show specific allergy to food substances should be desensitized only by mouth by giving daily increasing amounts of the food, but never enough to precipitate an attack. Occasionally a patient must be desensitized more than once. Temporary desensitization may be accomplished by giving a small amount of the substance by mouth three-quarters of an hour before meals. If the sensitizing substance is causing attacks by inhalation and cannot be avoided then desensitization may be attempted by injection of the substance in increasing amounts. However, as the great majority of cases do not show any specific allergy, but are sensitive to some agent peculiar to the climate in which they live, bronchial asthma is therefore a climatic disease, and can be successfully treated by changing the patients' residence. This does not necessarily mean residence at a high altitude, although patients are often greatly relieved by residence

in a high altitude, and can there be treated by non-specific antiallergic therapy. The author has used tuberculin for three years for the non-specific treatment of asthma, and finds it gives the most satisfactory results of the various substances tried. Almost all cases of asthma are sensitive to tuberculin and have a general reaction. Among 300 cases only 3 positive cases of tuberculosis were found. The dosage is difficult to determine. He begins with small amounts, gradually increasing until the patient is either free from complaints or a marked local reaction results or the treatment does not help. As soon as the patient is free from complaints injections are given once a week, later once in two weeks without increasing the amount or slightly increasing it. If a local reaction results and the patient feels better then each week a dose is given large enough to give a local reaction. If the patient feels worse then smaller doses are given. If large doses have been given without any results then a new series of injections is given, beginning with very small doses (1 to 100,000,000), and if this series gives no results then tuberculin therapy is useless. If the patient reacts strongly to tuberculin, or if tuberculosis is suspected, then the first dose given is 1 to 10,000,000. In other cases one can begin with 1 to 1,000,000. Old tuberculin (T. O. A. Koch) only is used. At first two injections a week are given subcutaneously, then one a week, and if the conditions are satisfactory one every two weeks and later one every three weeks. In favorable cases, after three or four months, only one injection in three weeks is given, and this is continued for one year. The tendency is to give too large doses, and small doses give the best results. In the first series of 200 cases 50 per cent were cured or almost cured; 38 per cent were improved; 12 per cent were uninfluenced. In the second series of 100 cases, which represented cases already treated with tuberculin by other doctors unsuccessfully, 60 per cent were cured or nearly cured, 25 per cent improved and 15 per cent unimproved. Cases which show return of symptoms after a year's treatment receive a second shorter series of injections. Cases in which climate plays an important role should be kept in their usual environment as much as possible. As tuberculin often gives results only after several weeks, quicker results may be obtained by injections of milk or sulphur in oil. The first milk injection is 0.1 cc subcutaneously; one hour later, 0.5 cc; the next day, 1 cc; then 5 or 10 cc intramuscularly. If the asthma is improved then the milk injections are continued, increasing the amounts 0.5 cc or 0.2 cc. This is continued for one week. After an interval anaphylaxis must be kept in mind, and only 0.1 cc given as the test injection. If there is no change during the fever period then milk therapy is of no use. Sulphur is given with the same object as milk, using a 1 per cent solution of precipitated sulphur in olive oil; 1 cc of a 1 per cent solution of sulphur injected intramuscularly will give a local and general reaction at the end of twelve hours, often with improvement of the asthma. The dose should be selected which will give relief of symptoms and not cause a too severe local reaction; 0.1 to 0.5 cc is often sufficient. Peptone has not given as satisfactory results as has tuberculin, and he considers intravenous injections dangerous in cases showing allergy. Vaccines and autovaccine therapy in asthma, he believes, is founded on wrong theories, as 85 to 90 per cent of his cases showed variation of symptoms with change of climate or stay in the hospital. He believes

that vaccines, particularly stock vaccines, may cause an improvement in the asthmatic symptoms just as is true of several diseases, and in his experience vaccines may cause an increase in the symptoms, while tuberculin gives better results. Patients are put on a purin-free diet because it has been shown that most of these cases have disturbed purin metabolism. Butter, milk and cheese are also prohibited. Carbohydrates are also restricted, and for a long time meat, fish, vegetables and eggs are the basis of the diet. Some cases of asthma have attacks six to eight hours after meals, and are free from attacks when fasting. To these cases rice, zwiebach and tea only are given, with gradual addition of other foods, until a diet is built up. Peptone by mouth is often given as a form of non-specific therapy. Three-quarters of an hour before meals 0.5 gm. of peptone is given and between meals nothing is eaten. This may be tried for a week and continued for one month if there is improvement. Adrenalin, in doses of 0.2 to 0.6 cc is the best substance to counteract symptoms of allergy when they are acute.

An Efficient Intestinal Antiseptic: The Perchlorides of Mercury and Iron in Combination.—WILSON (*Brit. Med. Jour.*, February, 1924, 1, 270) advocates the use of the perchlorides of mercury and iron as an intestinal antiseptic, and has used this remedy since 1894, when it was first brought to his attention by Wedgewood (*Brit. Med. Jour.*, May, 1894). In cases of enteric fever, colitis and dysentery he has used it extensively, with good results, and gave 15 minims of liquor hydrargyri perchloride and 15 minims of tinctura ferri perchloridi combined with glycerin and chloroform water three to four times a day. As albumins and alkalies destroy the antiseptic action of the perchloride of mercury, the drugs should be given before meals. Some cases have been known to take this mixture continuously for six months without injurious effects. In women it is advisable to omit the dose for a day or two before the menstrual period.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Use of Sulpharsphenamin in Vincent's Angina and Stomatitis in Children.—BARENBERG (*Jour. Am. Med. Assn.*, 1924, 83, 25) and his collaborator BLOOMBERG used this remedy in cases of Vincent's angina. They point out that there are some cases of stomatitis which are due to lack of antiscorbutic vitamin, and as cases of stomatitis and Vincent's angina have been reported as cured by giving adequate amounts of antiscorbutic vitamin, this protection should be definitely given all cases. In their series the authors gave adequate amounts of antiscorbutic vitamin. They feel that when the condition clears up with this

method that the Vincent's angina has been spontaneously cured as has been noted from time to time in cases of Vincent's angina. The first sign of cure is the subsidence of the adenitis, this swelling disappearing before the lesion itself. Under simple local treatment the glands remain enlarged after the ulceration is healed. It is important to remember that marked improvement in Vincent's angina and ulceromembranous gingivitis treated with intramuscular injections of sulpharphenamin is not apparent until the third or fourth day after injection. It has been shown that sulpharsphenamin exhibits its greatest parasitocidal effect three or four days after injection. The result in Vincent's angina are more remarkable than in gingivitis, because the former is usually more amenable to treatment. This treatment does not rid the mouth of fusospirillar organisms, which the authors found in smears from the gums and tonsils of many children with apparently healthy mouths. They found that sulpharsphenamin is a specific for fusospirillar infections of the mouth and throat, and that one or two injections usually cure. Intramuscular injections combined with local application of sulpharsphenamin hastens this result. In their experience no local or general reactions were encountered in fifty-one injections. This mode of therapy is particularly suitable, as intravenous injection is difficult in children. It is also of value in the treatment of pyorrhea.

The Effect of Tonsillectomy on the General Health of Twelve Hundred Children.—KAISER (*Jour. Am. Med. Assn.*, 1924, 83, 33) reviewed the data of twelve hundred tonsillectomies, and he feels that there is a great deal of value in the procedure, but that we must not be unmindful of the dangers of the surgical procedure, as well as of the complications that do occur. There is an impressive absence of spectacular results when the observations are controlled by observations on a group not operated upon. The desirability and justification of the operation depends on the ultimate effect on the child. Many years must elapse before the ultimate effect can be determined, but after a period of three years a group of twelve hundred children operated on were compared with an equal number of children not operated upon, and he observed that tonsillectomy offers a child considerable relief from such common complaints as sore throats, head colds and mouth breathing. It lessens the chances of having discharging ears and their complications. It assures some protection against glandular infection, but is no guarantee against it, and it does not assure the immediate disappearance of enlarged cervical glands. It does not influence favorably or unfavorably infections of the larynx, bronchi and lungs, as they occurred equally in the two groups. It does not prevent scarlet fever or measles, but may influence the severity of the infection. It seems to lessen the incidence of diphtheria by removing fertile soil for the diphtheria bacillus. It has not influenced the incidence of chorea or rheumatism. It has shown a lessened incidence of heart disease over a period of three years. It has definitely reduced malnutrition in the group operated upon as compared to the group not operated.

Postencephalitic Behavior Disturbances without Physical Signs.—BEVERLY and SHERMAN (*Am. Jour. Dis. Child.*, 1924, 27, 565) say that a sufficient number of postencephalitic behavior cases have been

studied to enable them to recognize a fairly constant symptomatology. A history of influenza or an undiagnosed condition with diplopia, a permanently developed strabismus, or a protracted period of somnolence is frequently obtained, and should immediately arouse suspicion. The mental and personality changes date from the illness or develop after a period of time even to several years. Personality changes manifested by a change in disposition, inability to sleep at night, violent outbursts of temper, irresponsibility, incorrigibility at school, hindrance in school work, cruelty to animals, lying and the like are the most frequent complaints. The delinquencies are nearly always committed alone and are influenced only slightly by changes in environment. Deterioration of intelligence, poor memory, and poor attention are nearly always reported by teachers and parents. The psychologic examination gives no evidence of mental deterioration. The attention and other mental capacities are normal, except for changes due to the emotional disturbances. The general impression after observing their behavior under examination is that the intelligence is low. The childish mannerisms, impulsive nature of the delinquencies, poor insight into their mental difficulties, the appearance of deterioration, are in marked contrast with the high rating obtained by intelligence tests. This is the most outstanding characteristic. All of these findings are referred to a definite time of onset. In a large percentage of children there is hyperactivity, irritability, alertness and marked emotional instability, the emotional tone varying from extreme anger to a cordial attitude in a few seconds. In a much smaller percentage of cases there was marked indifference, lack of initiative and sluggish body activity. Often there is a paroxysmal polypnea with the emotional outbreaks. In 1 case there was mental difficulty manifested by extremely slow comprehension. In another case there was marked weakness of the extremities which was the initial complaint.

A Comparison of the Metabolism of Some Mineral Constituents of Cow's Milk and of Breast Milk in the Same Infant.—WANG and DAVIS (*Am. Jour. Dis. Child.*, 1924, 27, 560) studied chlorid metabolism. They found that change of diet from breast milk to cow's milk was invariably followed by an increase in the chlorid excretion in both feces and urine and *vice versa*. The increase is due, at least in part, to the increased chlorid intake in cow's milk. The average intake with cow's milk was 1.4817 gm. per twenty-four hours and with breast milk 0.4441 gm. The average excretion in feces was 0.1128 gm. and 0.0576 gm. respectively, and in urine 1.0988 gm. and 0.3298 gm. The utilization of chlorid runs parallel to the urinary chlorid; with breast milk it is 0.3847 gm. per twenty-four hours and with cow's milk, 1.3691 gm. There is no marked difference in percentage utilization of chlorid intake between the two milks. For breast milk the average utilization was 87.4 per cent as against 92.2 per cent for cow's milk. There was great variation in chlorid retention in different individuals. The average retention for breast milk was 0.0886 gm. per twenty-four hours, or 19.2 per cent, and for cow's milk 0.2710 gm. or 18.9 per cent. As age increased there was a decrease in the actual retention of chlorid with cow's milk, but no such relation existed with breast milk. There was no definite relation between age and percentage retention. Change of milk had no

effect on the chlorid content of the blood. On a diet of breast milk the average blood chlorid was 627.7 mg. per hundred cc of blood plasma, and on cow's milk it was 618.1 mg.

The Effect of Fluid upon the Temperature and Blood Concentration in the New-born with Fever.—BAKWIN, MORRIS and SOUTHWORTH (*Am. Jour. Dis. Child.*, 1924, 27, 578) emphasize two points of interest. The striking parallelism between the effect of fluid on the blood concentration and on the temperature in the new-born with fever offers strong evidence in favor of the view that this particular type of fever is due to dehydration. The great efficacy of the oral over the subcutaneous or intraperitoneal routes in reducing the concentration of the blood and lowering the temperature in the new-born with dehydration is of great interest. When the fluid is given by mouth it enters the blood promptly as is indicated by a fall in the serum protein concentration and in the red cell count. When the fluid is given hypodermically or intraperitoneally the fall in blood concentration is neither so marked nor so prompt as in gavage. Apparently a process exists whereby fluid given by mouth is promptly absorbed into the blood and tissues. Fluid given into the subcutaneous tissues or the peritoneal cavity enters the blood much more slowly and to a much less extent. Similar results were obtained in older infants dehydrated as a result of severe diarrhea.

The Clinical Value of the Routine Examination of Blood Smears in the Diagnosis of Pertussis.—HEIMAN (*Arch. Ped.*, 1924, 41, 385) studied 300 cases of pertussis and suspected pertussis. He based his tests on a relative lymphocytosis. One hundred white cells, stained with Jenner's dye, were counted and for practical purposes a simple division, including only polymorphonuclear cells and lymphocytes, was made. The eosinophilic leukocytes were included in the polymorphonuclear and the transitional cells in the lymphocytes. Small and large lymphocytes were grouped together. The entire procedure takes but a few minutes. The first group included those cases that were unquestionably pertussis. The majority had a history of exposure to the infection. They all had the characteristic persistent spasmodic cough with frequent vomiting. In 75 per cent of the cases a distinct whoop was present. Of this group of 124 cases, 106 or 65.5 per cent showed a very definite lymphocytosis. The ages of this series ranged from three weeks to thirteen years. The second group of cases included those with suspicious coughs which later showed unquestionable symptoms of pertussis. They were all seen within the first two weeks of the infection, about half of them during the first week of the cough. Twenty five cases gave a history of exposure, while 59 did not. In the latter cases it was certainly not possible to venture a diagnosis from the history and physical examination alone. Of this group of 84 cases, 69 or 82 per cent showed a very definite lymphocytosis. In the third group of 57 cases including those with suspicious coughs which subsequently proved not to be pertussis, the patients were seen within about two weeks after the onset of symptoms. In each case the mother was asked to report if the cough became less marked or disappeared. In none of these cases did a whoop develop nor did the cough become progres-

sively worse. In this group are included only those whose subsequent course could be followed. Only 10 or 17 per cent of this group showed a lymphocytosis. The last group of pertussis suspects numbered 35 cases, and this group included those cases whose subsequent course could not be followed carefully enough to allow of any definite conclusions. The impression left by going over the incomplete results are in accord with the results obtained in the other groups. While the routine examination of these 300 patients did not bring forth any positive method of diagnosing pertussis, but the results emphasize the almost constant occurrence of lymphocytosis which should be an aid in the early detection of this infection.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

The Pyelitis of Pregnancy.—VAUX (*Am. Jour. of Obstet.*, 1923, 6, 681) analyzing records of patients suffering from the pyelitis of pregnancy, found that they were generally undernourished, somewhat anemic, and in some a hyperplasia of the thyroid gland was present; but in none was there serious defect or disease. Half of these patients had had their tonsils removed and the remainder showed no evidence of chronic tonsillitis. Their teeth were invariably poor and some had pyorrhea. In 3 cases there was evidence of cardiac lesions with normal compensation and none had serious pulmonary lesions. Some had previously had abdominal operations, and some had lacerations of the genital tract. All had vaginal discharges varying from a moderate thin white discharge to profuse mucopurulent leukorrhea. The Wassermann reaction was negative in all; only one gave a positive Neisserian reaction. Mixed infection of low grade was usually present. The histories showed that the condition began gradually, the patients having no treatment until it became severe enough to disturb the general health. One or both kidneys were usually involved. The writer is inclined to ascribe the occurrence of this complication of pregnancy to the combination of normal anatomical and physiological changes occurring in pregnancy; thus anatomically there is obstruction to the discharge of urine, leading to its accumulation in the pelvis of the kidney. Residual urine is usually present in the bladder during pregnancy. The right kidney was more often involved. The first symptoms of which the patients complained was usually frequency of urination. Anemia usually developed. The normal bladder reflexes varied greatly; in some there was constant tenesmus, while others had little desire to empty the bladder. The colon bacillus was always present, but one case showing streptococci. Cystoscopically hyperemia with a small amount of apparently cloudy urine dribbling into the bladder was found. There was no necrosis of the

bladder wall nor were there areas of hemorrhage, laceration or polypoid growth, nor calculi present. In one instance an abscess at the root of a tooth was present. The blood was usually of the type known as Group 4. There was no mortality among these patients and in but 1 case was labor induced at the seventh month. The treatment consisted essentially of rest in bed with milk and water diet. The Fowler or semi-Fowler position, the knee-chest posture, were used three times a day for five minutes, and patients were requested not to sleep habitually on the right side. Free catharsis was useful. Vaccination and intravenous medication were useless, annoying, and caused excessive reaction. Flushing the pelvis of the kidney was irritating and useless, while in severe cases with vomiting and general weakness, 5 per cent soda bicarbonate solution, one pint every six hours given in the bowel, was of definite value. In serious cases a subcutaneous injection of 500 cc of normal salt solution was valuable. Potassium citrate in large doses by mouth gave some relief of symptoms, while urotropin was without result. Opiates were used as needed. The removal of foci of infection was found to be useful and hot applications over the kidneys gave the patient comfort. A liquid diet at first, followed by an abundant and highly nutritious one was essential. The usual course of the complication was from seven to seventeen days before the temperature and pulse became normal and tenderness disappeared. Pus and bacilli were present, however, in the urine of these cases throughout the remaining months of pregnancy and sometimes after delivery. In the one case in which pregnancy was interrupted the patient grew rapidly better after the interruption. As a rule it is much better to make no cystoscopic examinations, to omit catheterization of ureters, to relieve the bladder of residual urine and when cystitis is present to irrigate the bladder with a mild solution. The writer believes that the real infection is primarily of hemotogenic origin, although the blood stream culture is invariably negative because of the high germicidal qualities of the maternal blood. Stress is laid upon obstruction in the lower urinary tract in promoting infection of the kidney and its pelvis.

A Difficult Diagnosis During Pregnancy.—CLIFFORD (*Brit. Med. Jour.*, 1923, 2, 1045) describes the case of a married woman apparently pregnant in whom the movements of the child had been active until two days before admission. She was apparently at full term, the fetal elements were very plainly to be felt, the head was high up and in the right occipo-posterior position, heart sounds and movements were absent. The cervix was protruding from the vagina and no presenting parts could be felt. A Roentgen-ray examination gave no information. There was slight rise of temperature and the cervix was cleansed, replaced and a ring pessary was inserted. As labor did not develop, the patient asked to leave the hospital. Three weeks later she returned with the same condition but a slightly higher temperature. An effort was made to induce labor by inserting bougies, but they could be passed but $3\frac{1}{2}$ inches although two attempts were made. The temperature was 102° F. and the pulse 120. A stock residual vaccination was administered and ten days later the abdomen was opened when a full term macerated fetus was found in a sac with the placenta almost entirely attached to the outer abdominal wall. The placenta was separated without bleeding, the membranes were not removed. The cavity was

drained and irrigated by the Carrel-Dakin method for three weeks. In six weeks nothing but a small sinus remained. On closely questioning the patient it was found that she had previously had severe abdominal pain with vomiting followed for five days by some vaginal hemorrhage. A surgeon had examined the patient who diagnosed appendicitis, but apparently operation was refused. The reviewer recently had occasion to study the case of a young woman, married five months, with a history of considerable emaciation, the last menstrual period being irregular and repeated with vague pelvic discomfort. On examination on the left side was an elastic mass which could not be differentiated from the uterus. The breasts were poorly developed. There was temperature of 102° F., the urine was normal. The emaciation of the patient and the history of cough suggested tuberculous infection; and the possibility of ectopic gestation was also considered. A Roentgen-ray examination of the abdomen and pelvis gave no information whatever. Physical examination of the chest gave roughened breathing without rales and no expectoration. There was a leukocyte count of 20,800. The patient had a moderate primary anemia. On section the pelvis was roofed over by chronic peritonitis with adhesions. There was peritonitis along the cecum. With considerable difficulty a mass on the left side was dissected with the fingers and from the floor of the pelvis a cystic body the size of a lemon was shelled out, whose wall contained some pus and whose cavity on opening revealed a dark chocolate fluid. The tube and ovary could not be distinctly recognized on the left side. On the right the ovary was bound down with a mass of adhesions, the identity of the tube had been lost in a chronic mass of exudate with numerous small cysts. The appendix could not be found. Drainage was introduced, stimulants given, but the patient became rapidly toxic, dying in forty-eight hours. At autopsy peritonitis was present, but from gross examination of the specimen removed and the body of the patient a positive diagnosis of the pelvic condition could not be made. There was no evidence of tuberculous infection in any part of the body. The appendix was high up behind the cecum and was subperitoneal. The pus was odorless and until a complete microscopic study of the tissues had been made, the exact diagnosis remained unknown. It was fair to infer from the general emaciation, the cystic character of the diseased tissues, the marked pelvic and cecal peritonitis, that a chronic infection or possibly the beginning of malignant degeneration of the ovaries was present. In many respects the history of this patient was typical of an early tubal gestation on the left side. Microscopic study of the tissues removed showed chronic tuberculosis of both Fallopian tubes.

Contraception.—In the *Journal of the American Medical Association* (1923, 81, 303) is an editorial based upon an article in the *Practitioner*, which devotes its entire July issue to the presentation of views of ten well-known British physicians on the subject of contraception. Economic and sociologic questions were discussed at the 5th International Conference held in London in July, 1922. At this time the opinion of those interested in the subject in Europe was freely expressed. In view of economic conditions in Europe at the present time, the subject is of especial importance because of the lack of population in some countries and the relative excess in others and the question of employment. In the British Isles the territory is limited by natural boundaries, and these

problems have become intensified during and since the World War. The physicians whose views are published discussed the physiologic and pathologic aspects of contraceptive methods, now generally known and available to the informed. Of the ten medical authorities, nine were in virtual agreement as to what constitutes the ideal method of contraception. The problem appeared to be to decide how the available information was to be brought to the attention of those most needing it and how such persons are to be encouraged to avail themselves of it. Under present conditions the tendency is to reach a new point of view upon this subject, with the presenting of reliable information, provided this can be done in the proper manner. Efforts have been made in the United States to publish such propaganda and such efforts have, in numerous cases, been resisted by the authorities. The obstetrical profession in the United States is not prepared at present to endorse this method, for many of the meetings held by those who are active in it, did not convince physicians who attended these meetings, that the information given was reliable or that the general effect upon the public would be good. Those persons who wish to avoid the responsibility of rearing children among the intelligent, well-to-do class are usually successful in so doing; they need no further advice upon the subject, many of them deliberately shirk their duty to the nation. Cases which appeal most to the obstetric profession for limitation of conception are seen in families of artisans or other workers, many of them professional persons of small and fixed incomes, where the size of the family has reached a point that the utmost exertions of the parents can provide for a decent life only, with few comforts and no luxuries. Among the poor many of these mothers become tuberculous or contract diseased conditions of the heart from infection and overstrain in caring for their children. The problem for the physician is to save the lives and health of these women and restore them with strength sufficient to care for their children. In the experience of the reviewer, obstetric surgery is the only reliable agency which can help such individuals. We now have successful methods of analgesia and local anesthesia so that we can terminate a threatening pregnancy and perform sterilization, leaving the ovaries and the uterus to continue the function of menstruation. The reviewer has a number of these cases in his records in whom the result of such operation has been largely satisfactory. He believes this method of birth control to be efficient, decent and justifiable in the case of multiparous women when further pregnancy threatens the health and life of the mother.

Severe Disturbance of the Heart Produced by Pregnancy.—SCHUBERT (*Zeitsch. für Geburtsh. und Gynäkol.*, 1923, 85, 593) describes the case of a patient, aged thirty-one years, who during her fourth pregnancy had great disturbance in the action of the heart with pain in the chest, dyspnea and prostration. In a subsequent pregnancy she became so much worse that at the third month she sought hospital care with the possible termination of pregnancy. On examination, an old mitral insufficiency of moderate degree was found, but the striking element in the case was the extreme irregularity in the action of the heart. The pulse-rate with the patient at absolute rest in bed varied from 170 to 80. The electrocardiogram showed extrasystoles, but the underlying cause of the irregularity was not elicited. Treatment was unavailing, the

patient became worse although for three weeks every effort was made to improve her condition and avoid the interruption of pregnancy. Finally under ether anesthesia, supravaginal hysterectomy was performed. The patient was discharged fifteen days after the operation with a pulse somewhat too frequent and irregular, but three weeks later her pulse was 70 and the electrocardiogram showed no abnormality. The Roentgen-ray picture of the heart was also normal. Whether this condition was the result of toxemia is an unanswered question. In the observation of the reviewer within a few months a patient, about eight months pregnant was sent into the Maternity Department of the Jefferson Hospital, suffering greatly from dyspnea and inability to lie down and sleep. Mitral stenosis with decomposition was diagnosed by medical consultants. The urine was practically normal, blood-pressure was low and the action of the heart so irregular and disordered that the sounds of the various valves could not be differentiated and a diagnosis of auricular fibrillation was made. Under rest in bed, digitalis and careful feeding and regular emptying of the bowels, the patient's physical condition very much improved. She then became disturbed mentally, refused treatment and became very difficult to control, she was transferred to the psychopathic ward of the Philadelphia General Hospital. She became more quiet and was then sent to the maternity department where she gave birth, without warning, to a living, slightly premature child. Labor was followed by attacks of cardiac syncope which were at first alarming; from this however, she rallied and insisted upon going to her home. Her mental condition never entirely cleared and she was practically uncontrollable. The ordinary tests for the toxemia of gestation failed in her case. There was no hemorrhage at labor and the condition of the heart seemed hopeless. Later the patient was admitted to the Medical Wards of the Hospital suffering from a severe pneumonia but this was weeks after the birth of her child and the pneumonia could not have been present while she was under obstetric observation. So far as medical tests were concerned there was no adequate explanation of her condition.

The Measurement of the Pelvis by the Roentgen Rays.—W. R. MACKENZIE (*Jour. of Obstet., British Empire*, 1923, 30, 556) contributes an interesting and well-illustrated paper upon this subject. He gives various measurements and includes two plates of pregnant patients one showing the fetal head about to engage five hours before the commencement of labor, the other showing a compression of the cranium in attempted labor with contracted pelvis. In order to procure accurate results he calls attention to the necessity of a standard plate for pelvic measurements. When such an investigation is made the patient must be radiographed in the same position as the standard plate with the same point of focus, the roentgen-ray tube at the same angle to and the same distance from the sensitive plate. If these precautions are taken the various pelvic diameters can be worked out and the variety of pelvic contraction, if present, can be shown. This is the least tiring and uncomfortable method for the patient, of measuring the pelvis. By the coöperation of the Roentgenologist and the obstetrician both maternal and fetal life can be conserved. In none of his cases thus examined during pregnancy was intrauterine death produced, nor was there any physical or mental maldevelopment in the newborn child.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, MEDICAL SCHOOL, UNIVERSITY
OF PENNSYLVANIA, PHILADELPHIA.

Operative Treatment of Uterine Prolapse. In the Mayo Clinic, according to MASSON (*Jour. Iowa State Med. Soc.*, 1924, 14, 174), cases of uterine prolapse which require operative treatment are divided into three main groups: (1) Those in which it is expedient to preserve the function of the pelvic organs; (2) those in which it is important to preserve the pelvic organs, but in which there are no contraindications to producing a sterile state; (3) those in which the patients are near or past the menopause, and there is no contraindication to removal of the uterus. In treating patients during the child-bearing period an attempt should be made to restore as nearly as possible the normal relations. Repair of lacerations is, therefore, preferable to amputation, and shortening of ligaments to making fixations, or radical changes in the anatomical relations. It is important to treat these patients as early as possible, not only to relieve the pain and discomfort, but to prevent the necessity of a more radical operation later. If a young woman has a prolapse of the first or second degree, and there is no indication for opening the abdomen, and external shortening of the round ligaments of the Alexander type, repair of the pelvic floor and in certain cases vaginal fixation or plastic operation on the anterior vaginal wall, has been found to be very satisfactory in the Clinic. However, opening the abdomen adds only slight, if any, risk to the operation, and permits the inspection of other abdominal organs, so that, of late a modified Gilliam internal shortening of the round ligaments has been the operation of choice in such cases. In cases of older women, especially if there is a large cystocele, a plastic operation on the uterine ligaments and repair of the pelvic floor will not be sufficient. In most of these long-standing cases it is not the low-lying uterus that causes the discomfort, but the associated cystocele or rectocele, and treatment should be instituted to relieve these conditions. If the cystocele is large, and the body of the uterus still remains in the pelvis, the most satisfactory operation that Masson has found is the interposition operation of the Watkins-Wertheim type. In many instances the cervix is elongated and high amputation is advisable. If the patient has not passed the menopause the Fallopian tubes must be ligated when performing this operation, to prevent further conception which might prove dangerous. As the degree of prolapse increases, the prospect of cure by the regular Watkins technic decreases, and the failures following this operation are in the main due to an unwise selec-

tion of cases. In cases in which the uterine prolapse is the chief cause of complaint, and the cystocele is not marked, fixation of the uterus and perineorrhaphy give very satisfactory results. If there is only a moderate amount of prolapse vaginal fixation of the Mackenrodt-Duhrssen-Winter type or fixation of the fundus to the anterior abdominal wall by any of the well-known methods is advisable, but if the relaxation is marked, and the uterus can be delivered through the abdominal incision the Kocher or Murphy method, or a partial hysterectomy and fixation of the stump, is advisable. In extreme cases total hysterectomy should be performed, and the vault of the vagina fixed to the abdominal wall. In prolapse of the third degree, in which the cervix to the level of the internal os protrudes from the vulva, and the body of the uterus is in the lower pelvic strait, the author believes that the most satisfactory operation is that devised by C. H. Mayo, consisting of a vaginal hysterectomy with lateral apposition of the broad ligaments, with round and uterosacral ligaments included, and stitching these ligaments into the opening in the uteropubic fascia in exactly the same manner as the uterus is used in the Watkins-Wertheim operation. In cases of complete procidentia the uterine ligaments give little or no support, unless the approximation is made high, and in doing this there is considerable danger of injury to the ureters. However, most of the recurrences of cystocele following the Mayo operation are due to failure to appreciate the necessity of firmly fixing the uterine ligaments into the defect in the uteropubic fascia; that is, fixing the approximated ligaments firmly under the bladder, leaving just sufficient space for the urethra to protrude under the pubic arch, and also anchoring them into the entire length of the anterior vaginal wall. In cases of procidentia in elderly women, and in cases of extensive recurrence following any of the recognized types of operations, partial obliteration of the vagina is justifiable, provided the patient understands exactly what it means. In all cases of uterine prolapse if the pelvic floor is lacerated or relaxed repair of the pelvic floor is indicated, no matter what type of operation has been done to support the upper pelvic diaphragm.

Total Versus Subtotal Hysterectomy as Operation of Choice.—For several years there has been quite a bit of discussion among gynecologists as to whether or not a total hysterectomy should always be performed whenever removal of the fundus is indicated. Those in favor of the total operation base their opinion on the fact that occasionally carcinoma develops in the retained cervical stump, and they state that the mortality of the total operation is only very slightly higher than that of the subtotal operation. From a study of the literature, as well as from personal investigation, BLACK (*Texas State Jour. Med.*, 1924, 19, 664) concludes that total hysterectomy is the operation of choice in all cases of suspected malignancy of the body of the uterus and in badly lacerated or diseased cervixes complicating fundal conditions requiring uterine removal. In the treatment of myomata total hysterectomy is the operation of choice only in women approaching or past the menopause or with diseased cervixes. In uterine myomata in young women, with apparently normal cervixes, especially if the patient has a large adherent fibroid, making a total operation hazardous,

a subtotal hysterectomy is the operation of choice. When an abdominal hysterectomy is indicated, with extensive inflammatory changes surrounding the uterus, or when the pelvic diaphragm is fixed and there is a diseased cervix, a subtotal hysterectomy with amputation of the cervix is the operation of choice. Vaginal hysterectomy is the operation of choice in cases of procidentia or in the fat or aged with vaginal relaxation or some prolapse. Vaginal hysterectomy is attended by a very small mortality rate in properly selected cases. Although it is commonly stated that there is very little difference in the mortality between subtotal and total hysterectomy, this fact only applies when the operations are done by experts. In general, the mortality in the hands of the average surgeon is 9.44 per cent for the complete operation against 5.29 per cent for the subtotal operation. Therefore Black correctly advises that the subtotal hysterectomy should always be the operation of choice in the hands of most men, and this fact should be taught in our medical schools.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO; TORONTO, CANADA.

AND

DE WAYNE G. RICHEY, B.S., M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY, UNIVERSITY OF PITTSBURGH; PITTSBURGH, PA.

A Scarlet Fever Antitoxin.—Although curative serums for streptococcus infections have been made by various investigators, the large dosages required would seem to indicate that any curative antibodies contained in these serums are present in low concentration. With the idea of producing a scarlet fever antitoxin, DICK and DICK (*Jour. Am. Med. Assn.*, 1924, 82, 12) immunized a horse by subcutaneous injections of sterile filtrate from broth cultures of the strains of streptococci that had produced experimental scarlet fever. After increasing doses of toxin, up to 250 cc, had been given, it was found that 10 cc of the serum contained antitoxin sufficient to neutralize twenty times the amount of toxin that produced nausea, vomiting, general malaise, fever of from 100° to 101° F. and a definite scarlatinal rash in susceptible adults. Concentration did not destroy the antitoxin. The authors feel that "The therapeutic value of the antitoxin can be determined only when the results of its use in a large series of carefully controlled cases are available."

Results Obtained with the Dick Test in Normal Individuals and in Acute and Convalescent Cases of Scarlet Fever.—Having conducted studies with the Dick test among normal individuals along lines similar to those carried out with the Schick test, ZINGHER (*Proc. Soc. Exper. Biol. and Med.*, 1924, 21, 293) found that the susceptibility by age

groups from birth to adult life corresponded closely to the percentage susceptibility to diphtheria, as shown by the Schick test. The reactions in the mother and offspring during the first six months of life were similar. The blood serum of a person giving a "negative" or a "pseudo" Dick reaction caused blanching of the rash and neutralized the test toxin, while that of a "positive, or a combined," reaction caused no blanching of the rash and did not neutralize the test toxin. The Dick test was positive, as a rule, during the first two days of scarlet fever, but became less positive toward the end of seven days and negative toward the end of ten to fifteen days, when the antitoxic properties began to appear in the patient's serum. The neutralization of the test toxin was found to be a more delicate index of the presence of antibodies in a serum than its property to cause blanching of a scarlet-fever rash—the Schultz-Charlton test. Four reactions were recognized with the Dick test—all of which correspond closely to the similar four reactions noted with the Schick test. These reactions are a positive, a negative, a pseudo and a combined. The positive reaction closely resembled at the end of twenty-four hours a positive Schick test which had reached its maximum on the third or fourth day. It appeared within six to twelve hours, reaching its height at the end of twenty-four hours and faded fairly rapidly. A good positive reaction was followed by pigmentation, with very slight or no scaling. The pseudo reactions were found to be due to the autolyzed bacterial substance of the streptococcus and other proteins in the test fluid. They were not specific, and could be separated from the positive reactions by a control test, using toxin neutralized with an equal amount of 50 per cent convalescent serum or of normal serum from negative Dick reactors. In a pseudo reaction the same appearance obtained with both the toxin and the control. It was most frequently encountered in old children, adults, and in some who gave a previous history of scarlet fever. The combined reaction showed a much more pronounced redness at the site of the Dick test as compared with the control test. The author considers that the positive and combined reactors are probably susceptible; the negative and pseudo reactors are probably immune to scarlet fever. The toxin was destroyed at 100° C. for forty-five minutes in dilutions of 1 to 100, so that in all probability the author will use the heated toxin for purposes of control, as in the Schick test. The positive reaction noted in all early cases of scarlet fever and the subsequent negative or pseudo reaction during convalescence in nearly all these patients would indicate that the different agglutinative strains of hemolytic streptococci found in the throats of scarlet-fever patients produce the same antitoxic antibodies. The Dick test was found very valuable for diagnostic purposes, as a positive reaction obtained during the first day or two of a suspicious scarlet-like rash and again two weeks or more after the fading of the rash indicated that the patient did not have scarlet fever. The author considers the Dick test of great value, with an increasing field of application in the selection of susceptible individuals for passive and active immunization, for passive immunization with convalescent serum from human beings or antitoxic serum from animals and for active immunization with increasing doses of the toxin itself. For active immunization the author is using 25, 50, 100 and 200 skin test doses, the injections being given intramuscularly about a week apart.

Further Studies on the Potency of Botulinus Toxin.—By titrating botulinus toxin from day to day, BRONFENBRENNER (*Proc. Soc. Exper. Biol. and Med.*, 1924, 21, 318) observed that determinations of the potency of dilutions of toxin in physiological salt solution frequently gave inconsistent results, due to the fact that NaCl, as well as many other salts of monovalent and polyvalent metals had a direct deteriorating effect upon the toxin. This effect was more marked the higher the dilution of the toxin, the longer the exposure and the higher the concentration of the salts. If the toxin were diluted in distilled water the results of titration were more regular. In the presence of low concentration of salts addition of serum or broth seemed to protect the toxin from deterioration. Toxin diluted directly in normal horse serum or in ordinary broth had an increased potency. In view of this, the author points out that it is important to determine carefully the type of toxin involved before administering antitoxin, as experiments have shown that animals receiving heterologous antitoxin (Type B), together with botulinus toxin (Type A), died more promptly than the controls receiving toxin alone.

Culture Filtrates of Hemolytic Streptococci from Scarlet Fever: Intracutaneous Reactions in Test Animals.—Employing the Dick toxic filtrate obtained from cultures of hemolytic streptococci from scarlet fever, WILLIAMS, HUSSEY and BANZHAF (*Proc. Soc. Exper. Biol. and Med.*, 1924, 21, 291) found that the intracutaneous injection of these filtrates in young depilated rabbits gave a very clear-cut reaction and that the filtrates were neutralized by serum from convalescent scarlet-fever patients. The reaction in guinea-pigs was not as clear cut as in the rabbits. The strongest and most lasting reaction in rabbits was obtained in the filtrates from a forty-eight hour growth. While the convalescent scarlet-fever serum seemed to neutralize the filtrates of the growth of the hemolytic streptococci from scarlet fever, as shown by the intracutaneous reaction in rabbits, it did not neutralize toxic filtrates obtained in the same way from *Staphylococcus pyogenes* or from *Escherichia coli*. Neither did it neutralize a toxic filtrate obtained from a hemolytic streptococcus from endocarditis, while it did neutralize one isolated from a wound infection, which had been included by absorption of agglutinins in our agglutinative group of hemolytic streptococci obtained from scarlet fever.

The Pathogenesis of Rheumatic Fever.—"It is surprising that in spite of the great advance in the knowledge of the causation of the most common infectious diseases, we still must recognize our uncertainty of the etiological agent in this infection (rheumatic fever). Certain contributing environmental factors have been suggested, and non-hemolytic streptococci have been claimed by several authors to be the causative microorganisms, but the failure to recover these streptococci from a majority of patients and the fact that the classical disease presented by man has not been reproduced by inoculating them into lower animals have caused most students to hesitate before considering the question settled." Consequently, to obtain a better understanding of rheumatic fever, SWIFT (*Jour. Exper. Med.*, 1924, 39, 497) has correlated the clinical findings of the patient with the examination

of the various tissues that can be obtained from the subject during life and after death. The gross clinical manifestations of rheumatic arthritis are pain, tenderness, swelling, redness and local heat diffusely distributed about the joint. The synovial fluid contains many exudative cells, mostly polymorphonuclear leukocytes. "Remarkable features to the acute arthritis are: (1) The tendency for the inflammation to migrate—to jump—from one joint to another without any apparent involvement of the intervening tissues; (2) the failure of the process to go on to suppuration; (3) the rapid disappearance of the symptoms and signs of inflammation after the patient has taken such antipyretic drugs as certain derivatives of salicylic acid or phenyleinchoninic acid." In fatal cases the most striking gross feature found at autopsy is the appearance of rows of small bead-like excrescences along the free margins of the heart valves. These verrucae are made up of coagulated elements derived from the circulating blood. Older verrucae show a definite tendency to heal, becoming covered with endothelium and invaded by organizing connective tissue. But even in the young lesions a distinct proliferative inflammation occurs in the substance of the heart valve. Although it is a moot point whether the destruction of the endothelium is primary or subsequent to an injury to the underlying tissue, it is not difficult to conceive of the primary injury of the valves occurring in their substance rather than on the surface—in which event it would be better to consider rheumatic disease of these structures as a *valvulitis* rather than a simple *endocarditis*. "The most generally recognized specific histological lesion of rheumatic fever is the so-called Aschoff body, which is a submiliary nodule located in the myocardium, usually in close relationship with the small bloodvessels." There is practically always a small central area of necrosis surrounded by peculiar cells, having vesicular nuclei and a cytoplasm that takes a granular red color when stained with methyl-green pyronine; usually many cells are present with multiple nuclei, forming a particular type of giant cell, different from that seen in tuberculosis. At times the bloodvessel lumina may be partially or completely closed by thrombi. The bloodvessels may also be constricted by pressure of Aschoff bodies or by an endarteritis, with swelling and proliferation of the endothelium, as seen in the smaller branches of the coronary arteries. The fibroid nodules in the subcutaneous tissue of children have a histological picture similar to that of the Aschoff body. They occur in the deep fascia over bony prominences and tendon sheaths and tendons. Not being in close opposition to nerves, they are usually painless. The joint lesions consist of focal lesions in the synovia, focal necrosis of the capsule, thrombosis of the smaller arteries and endothelial and perivascular reactions comparable with changes found in the heart and in subcutaneous nodules. The presence of many small nerves in the joint capsule and surrounding ligaments easily explains the great pain in rheumatic arthritis. In chorea minor, thrombi, endothelial proliferation and perivascular collections of round cells, together with small focal changes in the nervous tissue contiguous to these vessel lesions have been described. In summarizing the author says "It is evident that there are two distinct types of response on the part of the body to the infectious agent of rheumatic fever, viz, proliferative and exudative. The perivascular proliferative type of lesion, resembling an infectious granuloma, explains

the subacute and chronic character of the clinical symptoms in many patients with this disease. Marked exudation of serum into the peri-articular tissues and of serum and cells into the joint cavities are concomitants of the acute arthritis occurring with high fever and general intoxications; these acute exudations disappear following the administration of certain drugs. But their disappearance does not mean necessarily that all lesions of the proliferative type have resolved. In fact, we know that these last-mentioned lesions, when present in the subcutaneous tissues, often continue for months; and from analogy we may conclude that they have a similar persistent character in other tissues of the body invaded by the causative agent of rheumatic fever."

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

Syphilis as a Factor in the Etiology of Mental Deficiency.—WEISS and IZGUR (*Jour. Am. Med. Assn.*, 1924, 82, 12) state that it has become increasingly evident to them not only that syphilis is uncommon in mental defectives, but also that it is less common than in the general population, and is comparable in frequency only with congenital syphilis at any lying-in or child-caring institution. Their studies have led them to question whether there is any etiological relationship whatsoever between syphilis and mental deficiency. If syphilis is a cause of mental deficiency it should occur far more frequently in mentally deficient than in mentally normal children; the evidence adduced in their study controverts such an assumption. The feeling has grown more and more that there is no such abnormal mental state as "syphilitic amentia." It seems more than probable that syphilis is an incidental finding in mental defectives; if it bears any relationship to abnormal mental states in children it is recognizable as frank juvenile general paralysis or tabes. These conditions are not common; they are not, strictly speaking, amentias, but dementias, and they usually are not, or at least should not be, confused with primary amentia.

Influence of Lack of Vitamin C on Resistance of the Guinea-pig of Bacterial Infection, on Production of Specific Agglutinins and on Opsonic Activity.—WERKMAN, NELSON and FULMER (*Jour. Infect. Dis.*, 1924, 34, 447) state that the significance of the diet in maintaining a normal resistance to infection has lately assumed increasing importance.

In both human and veterinary pathology a lowered resistance has been shown to result when certain defective dietaries are employed. The vitamins, A and B particularly, have received considerable attention, although the significance of vitamin C has up to the present time remained more or less obscure. The authors find from their studies that guinea-pigs suffering from the lack of vitamin C experience a definite and determinable, though not marked, break in their resistance to infection by the pneumococcus and *Bacillus anthracis*. The reduced body temperature is of primary significance in accounting for the reduced resistance to infection. Guinea-pigs lacking vitamin C reveal no differences in their ability to produce specific agglutinins for the typhoid bacillus from that of healthy animals. Investigation of the phagocytic activities in guinea-pigs lacking vitamin C revealed no injury to the phagocytic mechanism as the result of vitamin-C deprivation.

Revived Activity of the Virus of Poliomyelitis.—FLEXNER and AMOSS (*Jour. Exper. Med.*, 1924, 39, 191) describe a strain of the virus of poliomyelitis which has passed through several stages of virulence, as tested upon monkeys. The first stage consisted of the adaptation of the original human virus to the monkey. In this process high virulence was readily achieved. The adapted virulent strain of virus was passed regularly through monkeys and maintained its activity for about three years, when diminution became apparent. The loss of power of the virus was such that it may be said to have returned approximately to the level of the original human virus. This change constituted the second stage. The third stage is represented by recovery of the high virulence. This revival occurred, it seems, during the sojourn of the virus in glycerol, and required several years for its consummation. It was first noticed nearly six years after the low level of the second stage became established. The potent virus of the third stage has been found to remain active over a period of at least four years while preserved in glycerol. What constitutes at least a superficial resemblance between the wave-like rises and falls of the incidence of epidemic poliomyelitis and the phenomena of increase and decrease in virulence of the specimen of virus has been alluded to. The two processes differ, however, essentially in respect to the time factor, since the fluctuations of the epidemic wave occupy small, and those of the virulence occupy large, increments of time.

Penetration of Normal Mucous Membranes of the Rabbit by *Treponema Pallidum* and the Influence of this Mode of Infection upon the Course of the Disease.—BROWN and PEARCE (*Jour. Exper. Med.*, 1924, 34, 645) carried out experiments with three strains of *Treponema pallidum* to determine whether infection could be produced by applying an emulsion, rich in spirochetes, to normal mucous membranes of rabbits, and whether an infection produced in this manner differed in any respect from one produced by other methods of inoculation. It was found that a simple instillation of a spirocheta emulsion into the conjunctival sac or the sheath was all that was necessary to obtain an infection. Still, the infection produced in this manner differed from that produced by intracutaneous or testicular inoculations, in that it tended to pursue a mild or asymptomatic course

and frequently without the development of a characteristic chancre. It is pointed out that these experiments may have a bearing on problems pertaining to obscure and atypical cases of human syphilis, as well as the more immediate question of the infectivity of *Treponema pallidum*.

Notes on the Longevity and Infectivity of Hookworm Larvæ.
—ACKERT (*Am. Jour. Hyg.*, 1924, 4, 222) states that hookworm larvæ (probably *Necator americanus*) lived eighteen months in a culture of cistern water. The temperatures to which they were exposed varied from 45° to 98° F., with fluctuations between 60° and 85° F. most of the time. Infectivity tests, made with an adaptation of the Goodey method, and with a live rat, showed that these eighteen-months-old larvæ responded to heat stimulation, but indicated that they were no longer infective.

Experimental Human Inoculations with Filtered Nasal Secretions from Acute Coryza.—ROBERTSON and GROVES (*Jour. Infect. Dis.*, 1924, 34, 400) secured nasal secretions from 11 persons suffering with acute uncomplicated coryza. After being diluted and passed through a Berkefeld filter, these secretions were sprayed onto the nasal mucosa of 100 volunteers. The authors state that their experiments presented no convincing evidence indicative of a filter-passing organism as the exciting factor in acute coryza, and believe the cases recorded as positive to be the result of factors independent of the inoculations. During an attack of coryza definite variations were noted in the bacterial flora of the secretions. During the onset and early stages of the attack there was a marked diminution of the total bacterial flora, with an equally marked predominance of one of the normal habitants—usually *Staphylococcus albus*. During the purulent stage of the attack a marked increase of all organisms over the normal flora of health was observed, although the predominance of one organism still remained. The later stages of the attack were marked by a gradual return to the normal flora of health.

Studies on the Relation between Tumor Susceptibility and Heredity.
—LYNCH (*Jour. Exper. Med.*, 1924, 39, 481) presents some of the results obtained from crossing mice from tumor strains with males from other sources. The comparison of the tumor incidence in the inbred and backcross daughters, though the numbers given are small, supports the theory that the tendency to develop neoplasms is hereditary and the frequency with which tumors appear in the first filial generation of such crosses, indicates that the character is dominant. Additional experiments involving larger numbers are in progress.

Is the Prophylactic Use of Diphtheria Antitoxin Justified? DOULL and SANDIDGE (*U. S. Pub. Health Repts.*, 1924, 39, 283) state that in Baltimore, according to the records of 508 consecutive cases of diphtheria, 10 per cent of the family contacts of ten years and under who were not given prophylactic antitoxin subsequently developed diphtheria, mostly within thirty days. Of the children of the same age group who were given prophylactic antitoxin only 1.2 per cent were

attacked. This experience is in agreement with the experience of other writers with regard to the low secondary attack rates among immunized children and the very much higher rates among children not so treated. At a case fatality rate of 2 per cent the risk of death from diphtheria undergone by unprotected children over that of children given prophylactic antitoxin is, for children of ten years and under, in Baltimore, 1 death to 568 family contacts. The best statistical record of deaths from antitoxin shows 1 death among approximately 75,000 persons injected. When, for any special reason, it is considered inadvisable to administer antitoxin as a prophylactic, the child should be guarded from infection by being removed from the infected home. On removal, such a child should be given the advantage of medical supervision and modern diagnostic methods. The evidence presented emphasizes especially the question of young contacts. It is realized that adults and older children may be subjected to daily examination, and possibly Schick tested. It is probable, indeed that in time this policy might be extended to all children of school age. Young children, however, constitute a special problem because of difficulties of examination and of diagnosis and because of much greater liability to attack. Among these children the use of prophylactic antitoxin is clearly not only justified but demanded.

Notice to Contributors.—All communications intended for insertion in the Original Department of this JOURNAL are received only *with the distinct understanding that they are contributed exclusively to this JOURNAL.*

Contributions from abroad written in a foreign language, if on examination they are found desirable for this JOURNAL, will be translated at its expense.

A limited number of reprints in pamphlet form, if desired, will be furnished to authors, *providing the request for them be written on the manuscript.*

All communications should be addressed to—

DR. JOHN H. MUSSER, JR., 262 S. 21st Street, Philadelphia, Pa., U. S. A.

THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

OCTOBER, 1924

ORIGINAL ARTICLES.

INFECTION OF THE GALL-BLADDER IN RELATION TO
PERNICIOUS ANEMIA

BY NOBLE WILEY JONES, M.D.

AND

THOMAS M. JOYCE, M.D.,

PORTLAND, OREGON.

(From the Departments of Medicine, Surgery and Pathology of the University of Oregon Medical School.)

SIX years ago, one of us (N. W. J.) began the study of the case of Mrs. G. (Case I) who gave a history of weakness and anemia that had existed in a periodically relapsing manner for seven years and was punctuated by occasional attacks of rather severe pain in the right upper abdomen. She presented a lemon-tinted skin, a moderate degree of glossitis and a blood picture possessing the so-called persistent characteristics of a pernicious anemia during the period between relapses; namely, a plus color index, irregular and large red blood cells with irregular staining properties but without nucleated red cells. She was studied for a month in hospital as a borderline anemia, that is, a probable pernicious anemia which at the time does not show the presence of megaloblastic cells, and because of the continued pain and soreness in the upper abdomen she was operated for chronic gall-bladder disease. This condition was found and the gall-bladder was removed. A hemolytic streptococcus was obtained in pure culture from it. During convalescence the lemon tint of the skin disappeared and the blood assumed, in the course of a few weeks, the picture of a mild grade of secondary anemia. The patient is a true general asthenic in build and state

of health; she has never been robust; is not strong now, but through two severe protracted illnesses during the past six years she has retained a general asthenic type of health and has not reverted to the picture of pernicious anemia.

The outcome of the treatment in this case suggested to the observer at the time as possibly of interest in throwing some light upon the hidden cause of Addison's idiopathic anemia, and since then all similar cases have been studied with this in mind. But the diagnosis of chronic cholecystitis could not be made with sufficient positiveness in other patients to justify exploratory operation, so that for several years there was no opportunity to study the question further. With the development of the newer technic of George and Leonard for the roentgenological study of the gall-bladder, however, the problem was taken up again. During the past year and a half several cases of borderline anemia and of frank pernicious anemia have been intensively studied from this standpoint. To our associate in roentgenology, Dr. Dorwin Palmer, we owe very much for the clinical recognition of existing gall-bladder disease in these patients. Operation on 2 of the patients depended wholly upon the roentgen-ray evidence. The gall-bladder in 1 instance appeared macroscopically normal but was removed because of the positive shadows obtained on the films and because of the anemia. The results of this study are now detailed.

A cursory review of the prominent points in the history of pernicious anemia is sufficient to impress one with the probability that the anemia, which bears this name, is a symptom-complex rather than a disease entity and that various hemolyzing agents may produce the picture if they have the opportunity to work within the body in a slow manner over a long period of time. In fact, clinical observation of any series of cases suggests the same thought, for the downward course is a very variable one. It may be rapid, comparatively speaking, without remissions and lasting only a few months; it may present the ordinary frank pernicious anemia course which continues two or three years and is characterized by several remissions and relapses in the meantime; and then again it may present the borderline picture which may continue for years and is a pernicious anemia in all appearances save that of not having megaloblastic cells in the circulation. This variable clinical picture was noted by Addison¹ in 1855 and more in detail by Biermer² in 1872. William Hunter has maintained since 1890 that oral sepsis constitutes the source of the hemolyzing agent and that the tongue and the stomach and intestinal mucosa become infected secondarily. In a British Medical Association Lecture in 1921, Hunter³ makes the statement that the tongue in true pernicious anemia has become by reason of the oral sepsis the actual focal site for the infection which causes the disease and suggests the name of "glossitic anemia" for it. He does not offer evidence substantiating this belief.

The first important contribution to the etiology of a pernicious type of anemia was that of Schaumann and Tallqvist⁴ (1898) who found a hemolytic substance in the head and body of the fishworm, *Bothriocephalus latus*, and proved that it was the cause of the pernicious type of anemia in persons infected with this parasite. Schaumann⁵ had already (1894) reported a study of 72 cases of fishworm anemia and had found the same clinical picture and the same megaloblastic metamorphosis of the bone-marrow as seen in true Addisonian anemia. The red blood cells averaged 131,100 per cm. in men and 1,272,000 per cm. in women. The bloods of all the patients showed megaloblasts in the circulation. Most of them had chronic achylia gastrica. The same changes were produced in dogs by feeding them extracts of the worms. Faust and Tallqvist⁶ determined that this hemolytic substance is oleic acid and that it owes its hemolyzing property to the fact that it is an unsaturated fatty acid.

The clinical picture and the morbid anatomy of uncinariasis anemia may be identical with that of true pernicious anemia (Ashford and King⁷). The hemoglobin content has been as low as 8 per cent (Dare and v. Fleischl) and the red blood cell count as low as 754,000 per cm. These extreme instances are associated with megaloblasts and the other characteristics of pernicious anemia. Eosinophilia is variable. The more severe the intoxication the fewer the eosinophiles; they may be absent. These authors state that eosinophilia shows a corresponding degree of resistance to the toxin. The bone-marrow may also show the same gray-red appearance and the same changes microscopically as in pernicious anemia, but usually also numerous eosinophilic myelocytes and myeloplaxes are present. Whipple⁸ quotes Preti as having found a hemolytic substance in Old World hookworms, which the latter believes to be related to the lipoids and to be similar to the hemolysin of *Bothriocephalus latus* found by Faust and Tallqvist. Whipple⁸ has found a weak non-specific hemolysin in New World hookworm which is soluble in salt solution, is destroyed by heat, and may be obtained in concentrated extracts from the bodies of the worms. The hemolysin acts on human blood and on that of laboratory animals. Whipple does not believe, however, that this weak hemolysin has much to do with the anemia of uncinariasis but that it is produced in the main by the direct extraction of blood from the bowel wall by the parasites, inasmuch as whole and partly disintegrated red blood cells floating in a bloody fluid are passed out from the intestinal tracts of the worms. From the work on experimental anemia of Bunting, who found that he was unable to produce a megaloblastic anemia by means of repeated hemorrhages alone, one would be inclined to believe that the hemolysin of the hookworm must play a role in the megaloblastic picture found at times in man.

Bunting's⁹ work (1905-1907) on experimental anemia is instructive. He produced what seemed like true pernicious anemia in rabbits and dogs by repeated small intravenous injections of ricin and of saponin. He was unable to produce such a type by repeated small hemorrhages, which caused a secondary type with an occasional normoblast in the blood-stream, the bone-marrow never showing evidence of injury. In producing a pernicious type of anemia by means of hemolytic agents, it was necessary to place them into the circulation in sufficiently large quantities to saturate the red cells in the blood-stream and to exert a direct harmful influence on the erythrogenetic centers of the bone-marrow, which alone leads to a megaloblastic metamorphosis. He concludes (a) that a secondary anemia due to a toxin, as for instance, that of tuberculosis, is found when the toxin is taken up by the red cells and the bone-marrow is left free to regenerate; and (b) that a pernicious type of anemia is found when the toxin injures the erythrogenetic centers in varying degree and prevents a normal regeneration. An imperfect and often a short-cut regeneration leads to the formation of immature and megaloblastic cells, both of which may then be found in the marrow and in the blood-stream. It is produced only when the toxin is introduced in sufficiently large quantities. Thus a severe secondary anemia may assume a pernicious type. The red cell crises then are expressions of severe injury to the bone-marrow rather than of regeneration. Thus, Bunting believes that true pernicious anemia is due to some primary hemolyzing agent circulating in the blood and affecting the bone-marrow secondarily. The marrow change is not the primary lesion. He believes both Bothriocephalus latus anemia and experimentally produced anemias seem to prove this statement.

Madler¹⁰ (1913) produced crises of pernicious anemia in rabbits by feeding them large quantities of olive and cotton-seed oil. He believes that the toxicity depends on the amount of unsaturated fatty acids and that the anemia is produced in the peripheral circulation by its direct attack on the red cells. The effect on the bone-marrow he believes to be due to the excessive demand placed on it. One may easily believe, however, that, if the hemolyzing agent of Bothriocephalus latus is oleic acid, an unsaturated fatty acid, and if the toxic substance of olive or cotton-seed oil is the same, the action of the hemolysin on the bone-marrow centers may be direct, as Bunting maintains, if there is a sufficient quantity present in the circulation.

The hemolytic action of the spleen as a causative agent in pernicious anemia need be mentioned only in passing. Eppinger¹¹ and v. Decastello¹² brought forth this opinion independently in 1913. It led to splenectomy in a number of persons with pernicious anemia. One of us (N. W. J.) studied 7 such patients before and after operation without seeing any material change from the

ordinary variable clinical course. The procedure has now been abandoned.

Association of pernicious anemia and chronic gall-bladder disease has been noted in medical literature from time to time. Probably Georgi¹³ (1887) was the first to mention it in a rather detailed report of a case presenting a frank pernicious anemia, gall stones being found at autopsy. This report called forth at once a retort from Ewald¹⁴ who cited the autopsy of another patient dead of pernicious anemia, in whom no macroscopical evidence of gall-bladder disease was found. Percy¹⁵ (1916) reported 37 cases of pernicious anemia operated upon for the removal of the spleen. The gall-bladder was removed twenty times for chronic cholecystitis and the appendix seventeen times because of chronic inflammation. In 9 cases the spleen, gall-bladder and appendix were studied bacteriologically. Hemolytic streptococcus was obtained seven times from some of these tissues, the *Streptococcus viridans* four times and the *Staphylococcus albus* once. The colon bacillus was also found in 5. Percy states that 58 per cent of 24 cases "were clinically in good condition" at varying intervals of time. One at the end of two years and eight months "is clinically perfectly well and carries no evidence of pernicious anemia in her blood, except that an occasional normoblast can be found." Later reports from this series of cases have not been obtained. Splenectomy was performed as the primary feature of the treatment, and removal of the gall-bladder and appendix was done as a part of the general process of ridding the body of septic foci, along with septic teeth and tonsils. Giffin and Bowler¹⁶ (1923) in a review of 628 cases state that 108 cases were associated with other diseases and that of this number 10 had had the clinical diagnosis of gall-bladder disease in addition to that of pernicious anemia. None of these patients came to operation. They state "On clinical examination no very convincing evidence of the condition (gall-bladder disease) is found."

This brief summary of the history of what is known regarding the etiology of pernicious anemia leads us now to recounting the following case records. Analysis of the important points in them will be discussed later. The pathological studies have been made by W. C. Hunter of the Department of Pathology with the counsel and aid of Dr. Benson, head of the department.

Case Reports. CASE I. Mrs. G., aged forty-five years, five para, three children living, was first seen June 6, 1917, complaining of general weakness, exhaustion, loss of weight and irregularly recurring attacks of pain and soreness in the upper abdomen, associated with constipation or, at times, bowel looseness. She had never been strong, but seven years ago she suffered a postpartum hemorrhage, since which time she has had a pale skin. At first it was a white

paleness; some years later it became lemon tinted, a color noticed by herself and her family. There were periods when she had numbness of the extremities. She had had measles, scarlet fever and sore throat earlier in life. At twenty all of her teeth were extracted, presumably for sepsis. Her family history was negative.

Examination. The patient is of a slight, asthenic build, moderately lemon-tinted skin, no jaundice. There is a moderate glossitis, a hemic heart murmur and some epigastric tenderness. The stomach acidity is 20 to 32; well chymefied food, and no blood. The stools show some blood from small hemorrhoids; no parasites. Five blood examinations, while in hospital from June 27 to July 17, gave practically the same findings; hemoglobin 80 to 85 per cent; red blood cells 3,680,000; white blood cells 7000; differential count: polymorphonuclears 65 per cent; small mononuclears 33 per cent; large mononuclears 4 per cent; transitionals 2 per cent; nucleated red blood cells negative; anisocytosis, poikilocytosis and polychromatophilia present; Wassermann negative.

Treatment. The patient was treated as a borderline anemia case, *i. e.*, a pernicious anemia which did not show nucleated red blood cells in the circulation. Receiving no relief from abdominal distress, she was operated upon July 20, on the assumption that she had a chronic gall-bladder disease. A large, distended, chronically infected gall-bladder was removed. The bile was greenish in color and contained much sediment. A hemolytic streptococcus was obtained from the gall-bladder wall. The appendix showed a moderate degree of obliterative inflammation.

Course. During the succeeding few weeks the patient improved slowly, as the general asthenic always does; her skin became clear and more or less pink in color. August 27, hemoglobin was 90 per cent; red blood cells 4,100,000; white blood cells 7100 with normal differential count. Irregular red blood cells and poikilocytes were present but polychromatophilic staining not. No nucleated red blood cells had been seen in six examinations. May 11, 1918, blood examination was recorded as follows: Hemoglobin 85 per cent; red blood cells 5,250,000; white blood cells 6300 of normal differential count. A few irregular red blood cells were seen but no irregular staining. In 1921, the patient suffered a supposed influenzal infection and some form of epidemic jaundice; at least, other members of the family and of the community had similar attacks of jaundice. As a result of this infection she was ill and weak for several months. May 3, 1921, blood examination showed hemoglobin 80 per cent; normal red cells 4,000,000; white blood cells, 9650. In 1922 the patient was ill, in and out of bed, with a sinus infection for nine months. On March 21, 1923, three blood examinations gave hemoglobin 80 per cent; red blood cells 4,500,000; white blood cells 6450 with normal differential count. There were some slightly irregular red blood cells but the general appearance of the blood

was that of a mild secondary anemia. The patient, herself, felt quite well, weighed 125 pounds, the skin was clear and the tongue showed no particular evidence of inflammation or atrophy.

Comment. The symptoms and physical findings in this case were those of a so-called chronic borderline anemia; an anemia characterized by the presence of the toxic or inflammatory symptoms of pernicious anemia and a blood picture possessing the permanent characters of pernicious anemia blood; namely, a plus color index and irregular shapes, sizes and staining properties of the red blood cells; but showing no nucleated red blood cells in the circulation. In addition to this, certain symptoms permitted the diagnosis of gall-bladder disease. The gall-bladder was removed and a hemolyzing streptococcus was obtained in pure culture from the wall. Six years have elapsed since the operation. The patient is fairly well. She has not progressed as a case of true pernicious anemia and the blood picture has regained fairly normal characteristics.

CASE II.—C., aged fifty years, was first seen February 7, 1916. For two years he had suffered spells of weakness, paleness, numbness and burning of the hands and feet, muscle soreness, constipation and distress in the abdomen and a mucous discharge from the nose. During the intermissions he has regained moderate health.

Examination. Heavy, gaunt type of build, pale, lemon-tinted skin and mucous membranes; no icterus; former dental sepsis; hyperplastic ethmoiditis with obstructing septal deflection. Stomach analysis shows complete achylia. The stools contain neither blood nor parasites. During February and March, 1916, while under treatment for pernicious anemia, the blood showed hemoglobin 73 to 90 per cent; erythrocytes, 2,420,000 to 3,480,000; leukocytes, 9000 to 4350; polymorphonuclears, 80 to 65 per cent; small mononuclears, 16 to 24 per cent; large mononuclears, 1.5 to 7 per cent; transitionals, 1 to 3 per cent; basophiles, 0.5 to 1 per cent; myelocytes, 1 to 1 per cent; normoblasts 2 cells found, megaloblasts negative; anisocytosis, poikilocytosis and polychromatophilia present. September 20, 1916, the hemoglobin was 100 per cent; erythrocytes, 5,280,000; leukocytes, 8600; 1 normoblast, fewer macrocytes and less irregular staining of the red cells was noted than formerly. In 1917, the patient spent four months in Johns Hopkins Hospital under treatment for pernicious anemia. September, 1921, four blood examinations showed hemoglobin 90 to 95 per cent; erythrocytes, 4,264,000 to 5,000,000; leukocytes, 6800; no nucleated red cells, moderate polychromatophilia and some macrocytes. July 19, 1922 to August 29, 1922, while under treatment, the hemoglobin was 60 to 82 per cent; erythrocytes, 1,240,000 to 3,370,000; leukocytes, 3200 to 6400. There were no nucleated red cells but marked variation in size and staining was present.

Positive roentgen-ray shadows of the gall-bladder were obtained July 19, and August 31.

Treatment. The patient was treated four times in hospital for pernicious anemia during these six years. Cholecystectomy and appendectomy were made September 7, 1922 (by T. M. J.).

Pathological Report. The wall of the gall-bladder is slightly atrophied. The mucosa is bile-stained and appears atrophic. Sections disclose a thinning and scarring of the wall and atrophy of the mucosa. Sections stained for bacteria reveal the presence of a few groups of organisms looking like staphylococci. A few diplococci are also present.

Pathological Diagnosis. Chronic atrophic cholecystitis.

Course. Convalescence from the operation was prompt. The lemon-tinted color of the skin cleared quite rapidly, the nail beds and mucous membranes showing pink. Fourteen blood examinations during the month in hospital showed a fairly graduated transition from the pernicious picture to a moderate secondary anemia. The last one, October 11, 1922, showed hemoglobin, 90 per cent; erythrocytes, 4,300,000; leukocytes, 8100; polymorphonuclears, 61 per cent; small mononuclears, 32 per cent; large mononuclears, 4 per cent; transitionals, 1 per cent; eosinophiles, 2 per cent; nucleated red cells, negative; very slight changes in the character of the red cells.

A month after operation the numbness and hurting of the legs and arms and at times over the entire body became worse. Since Christmas these symptoms have slowly abated and do not bother the patient as much now. He has returned to his work as a timber bruiser but is not yet strong enough to stand hard work. He feels, however, that he is gaining in strength progressively. Examination on May 5, 1923, revealed a physical state quite different from that seen at any time during the past seven years. The patient's color is good; the skin is red from his out-of-door life, and there is no evidence of sallowness or lemon tinting. The tongue shows a moderate glossitis but is not sore. The knee kicks are absent. There is slight swaying of the body with the eyes closed but no distinct incoördination. The patient states that a certain unsteadiness at night is less now than it formerly was. Four blood counts show hemoglobin, 88 per cent; erythrocytes, 4,570,000; leukocytes, 5200; with normal differential count. The red blood cells are well stained. There are a few macrocytes, and in the four examinations 1 normoblast is found. Undoubtedly the blood still possesses slight evidence of its former pernicious type but it approaches more nearly the picture of normal blood than it has done since the patient was first seen in 1916. His general health and strength is also better.

Comment. This patient had suffered for about eight years with the symptoms of a slowly progressing frank pernicious anemia

before the diseased gall-bladder was recognized and removed. A certain degree of change had taken place in the spinal cord as evidenced by the severe paresthesiæ, the loss of deep reflexes and a slight Rombergism. Since the operation the patient has regained much of his former health and the cord symptoms seem to be lessening. How much permanent damage has been suffered by the spinal cord and the erythrocytic centers of the bone-marrow only time will tell. Cultures from the gall-bladder were not obtained. Micro-organisms possessing the morphological characters of a staphylococcus and a diplococcus were found, however, in stained sections of the gall-bladder wall. Nine months have elapsed since the patient was operated upon and he seems to be progressively moving away from the picture of pernicious anemia rather than downward as seemed to be the one prospect in the summer of 1922.

CASE III.—Mrs. K., aged twenty-nine years, 4 para, was received January 29, 1923. She had suffered from recurring periods of weakness, paleness, nausea and constipation since scarlet fever at twenty years of age. Her skin had been of a sallow type of paleness since this time, but following a miscarriage in June, 1922, it has become a more pronounced lemon tint and the weakness and distress more severe. She has suffered slight paresthesiæ. Her history revealed typhoid fever at eighteen, measles in childhood, scarlet fever at twenty, influenza at twenty-six, two miscarriages and a phlebitis of the right leg.

Examination. Extreme asthenic type of build, weight 116 pounds, skin lemon tint and pale, severe dental sepsis; the tongue shows a blotchy glossitis; the stomach complete achylia; the gall-bladder gives faintly positive shadows on the films, and there is no indirect roentgen-ray evidence of gall-bladder disease. The stools are negative for blood and parasites. Nine blood examinations during a month in hospital showed, on an average, hemoglobin, 80 per cent; erythrocytes, 3,990,000; leukocytes, 12,000 to 6800; no nucleated red cells, anisocytosis, poikilocytosis and polychromatophilia present. The extraction of all teeth did not change the blood picture. Blood Wassermann was negative.

Treatment. After one month in hospital with bed rest, arsenic, hydrochloric acid, and so on, the patient was operated upon March 5, 1923 (by T. M. J.). The gall-bladder did not reveal any gross appearance of disease. The lymph nodes along the common bile duct were not enlarged. The common bile duct, itself, seemed to be somewhat dilated. In spite of the normal appearance and because of (a) the positive roentgenological evidence and (b) the type of the patient's anemia, the gall-bladder was removed. The appendix showed more evidence of disease and was also removed.

Pathological Report.—The gall-bladder wall is slightly thickened and fibrous. The mucosa is bile-stained and atrophic. Sections

disclose a desquamation of the epithelium of the mucosa; slight diffuse fibrous increase in the muscular coats and the rest of the wall. In the sections stained for presence of bacteria a few microorganisms resembling staphylococci are found. Cultures of the wall of the gall-bladder yield a slightly hemolytic *Staphylococcus albus*. Cultures of the bile are negative.

Pathological Diagnosis. Slight catarrhal cholecystitis.

Course. The patient convalesced quite rapidly from the operation; within one week the lemon tint of the skin was fading rapidly. On March 27, 1923, the blood showed hemoglobin, 89 per cent; erythrocytes, 4,700,000; leukocytes, 6000; polymorphonuclears, 69 per cent; small mononuclears, 24 per cent; large mononuclears, 4 per cent; eosinophiles, 1 per cent; basophiles, 1 per cent; transitionals, 1 per cent; nucleated red cells, negative; poikilocytes few, macrocytes negative, polychromatophilia absent.

May 5, 1923, the patient was again examined. She states that she feels stronger and has a desire to work for the first time since she became ill. Numbness in both hands lasted for a week after she went home but has not returned. The skin is now pale pink in color; it has lost its lemon tint. The septic tonsils still remain; they are to be removed later. The blood shows in four counts—hemoglobin, 75 per cent; erythrocytes, 4,540,000; leukocytes, 7000; of normal differential count. The red cells stain uniformly with pale centers. There are no macrocytes and no nucleated red blood cells are seen. The picture is that of a moderate grade of secondary anemia.

Comment. The transformation of this patient's blood picture after cholecystectomy from a pernicious type to that of a secondary anemia was quite rapid. A gain in general health has been quite as rapid also. From the gall-bladder wall *Staphylococcus albus* was obtained in pure culture and cocci resembling staphylococci were found also in stained sections. Although this patient is a general asthenic of marked degree, her progress toward recovery has seemingly been more rapid than that seen in Case II. It is possible that the pernicious anemia in this case has existed for only one year.

CASE IV.—H., aged sixty years, farmer, was received April 13, 1923. Paleness, weakness, shortness of breath and pains in the shoulders began one and a half years ago together with numbness in the ankles and knees, wrists and hands, and tingling of the toes and fingers. The patient has not lost much weight.

Examination. The skin is pale and lemon tinted. The mucous membranes are pale. The tongue is pale and glossy. The lower teeth and tonsils show infection. An upper plate is worn. The upper teeth were removed for sepsis. A hemic murmur is heard over the precordium. The stomach shows complete achylia. The

stools are negative. The antrum of the stomach is spastic. The bulb of the duodenum is drawn slightly to the right, and the lesser curvature margin is hazy. Films of the gall-bladder show positive shadows without stones. The blood Wassermann is negative.

Treatment. Ten blood examinations were made during four weeks in hospital under treatment. The first one showed: Hemoglobin, 40 per cent; erythrocytes, 1,780,000; leukocytes, 8850; polymorphonuclears, 35 per cent; large mononuclears, 6 per cent; transitionals, 1 per cent; eosinophiles, 1 per cent; normoblasts, 2; megaloblasts, 1. Many macrocytes and marked polychromatophilic staining was present. The last examination before operation showed: Hemoglobin, 71 per cent; erythrocytes, 2,450,000; leukocytes, 3600; 1 normoblast; polychromatophilia and anisocytosis were less marked than on entrance.

Cholecystectomy May 14, 1923 (by T. M. J.). Recovery from the operation was uneventful. The gall-bladder showed macroscopically little change from the normal. A small section of the liver was removed for examination. The change in the appearance of the patient during the first week was marked. The lemon tint of the skin disappeared quite completely and was replaced by a pink color. The blood showed: Hemoglobin, 76 per cent; erythrocytes, 3,080,000; leukocytes, 7200; polymorphonuclears, 72 per cent; small mononuclears, 14 per cent; large mononuclears, 9 per cent; eosinophiles, 4 per cent; transitionals, 1 per cent. The red cells stained fairly evenly and there were but few macrocytes.

Pathological Report. The gall-bladder is of average size, wall slightly thickened and scarred, mucosa intact, no concretions, contains about 15 cc of light brownish viscid bile.

The clipping from the liver measures 0.5 by 1 cm. and appears normal.

Microscopically there is a slight increase in the fibrous tissue throughout the wall of the gall-bladder. Scattered through the scar tissue are moderate numbers of small round cells. The mucosa is partially desquamated but the greater portion is intact and shows no noteworthy changes. Sections stained for bacteria disclose the presence of small numbers of organisms occurring in pairs and short chains.

Diagnosis. Slight chronic diffuse cholecystitis.

Bacteriological Findings. Cultures from the gall-bladder in meat infusion broth enriched with blood disclose the presence of non-hemolytic *Staphylococcus albus*. Whether this is a contamination from the skin of the patient or not is difficult to determine. No other microorganisms are found.

Bile. Sterile.

From the bit of liver tissue, alpha-hemolytic streptococcus, producing definite greenish zones about the colonies and occurring in both short and long chains, is isolated in pure culture.

Comment. The clinical appearance and the megaloblastic blood picture of this patient is typical of a true progressive pernicious anemia. The change in the general appearance of the patient, the rapid clearing of the skin and the equally rapid change in the condition of the red blood cells is seemingly more marked than that noted in the former three patients. The finding, however, of non-hemolytic organisms in the liver tissue and morphologically similar organisms in the wall of the gall-bladder brings up the question whether the anemia may be produced by the effect of some chemical substance entering the circulation from the infected gall-bladder rather than from the direct lytic action of the bacteria and their products on the red blood cells and the erythrocytic centers of the bone-marrow. A similar organism was obtained at autopsy in Case VIII. A portion of liver tissue was cultured for the first time in this case. The organism obtained in pure culture bears resemblance to the morphological characteristics of that found in the stained sections from the gall-bladder wall.

CASE V.—Mrs. J., aged thirty-seven years, 2 para (1 miscarriage at three months, seven years ago) was received December 7, 1922. Patient complained of periodic weakness and paleness which began after a miscarriage seven years ago. For the last three years the spells have been especially severe, but during the summers she has partially regained health. She suffered from loss of weight and strength, shortness of breath, swelling of the feet, nausea, vomiting and constipation and numbness of the hands and feet.

Examination. There was found pale, lemon-tinted skin, dental plates (history of previous sepsis), moderate glossitis, hemic murmur over the precordium, edema of the legs, complete achylia and stools negative to blood and parasites. The urine, blood chemistry and blood Wassermann are negative. Positive shadows of the gall-bladder are obtained December 18.

Eight blood examinations from the 8th to the 29th, inclusive: December 8, the blood showed hemoglobin, 20 per cent; erythrocytes, 1,550,000; leukocytes, 5200; polymorphonuclears, 67 per cent; small mononuclears, 29 per cent; large mononuclears, 2 per cent; transitionals, 1 per cent; eosinophiles, 1 per cent; occasional normoblasts, no megaloblasts; anisocytosis, poikilocytosis and polychromatophilia was present. December 29, the blood count was hemoglobin, 10 per cent; erythrocytes, 440,000; leukocytes, 6600; polymorphonuclears, 59 per cent; small mononuclears, 40 per cent; large mononuclears, 1 per cent; normoblasts were present; megaloblasts 1, the changes in the red cells more pronounced than before.

The first megaloblast was found on December 22, 3 were found on the 26th, and 1 on the 29th. Death occurred December 29, 1922.

Autopsy. The body of a white female, aged thirty-seven years. There is a general pallor of the skin, teeth absent, gums smooth,

subcutaneous fat is light yellowish and finely lobulated. Lymph nodes in root of mesentery are hyperplastic. Mucosa of stomach pale and atrophied. Small hemorrhages are numerous beneath capsule of liver. Liver parenchyma is pale and friable and the blood which exudes is pale.

The gall-bladder is free from adhesions; its wall is slightly thickened and opaque. The bloodvessels beneath the serosa are unusually prominent. Bile is dark greenish-black and viscid. The mucosa is bile-stained but apparently intact. The biliary lymph nodes are slightly hyperplastic. Petechial hemorrhages are found in the serosa of the pancreas. Spleen is about one-third larger than normal, cut surfaces reddish, moderately firm and somewhat fibrous. Kidneys are pale and anemic. Heart is yellowish-brown and flabby, no valvular lesions. Lungs are unchanged. There is marked hyperplasia of the bone-marrow.

Microscopically. The muscle fibers of the heart are rather shrunk. A yellow pigment appears in most of the cells lying between the fibrils and especially around the nuclei. Some of the cells are vacuolated and appear to have contained fat droplets. There are no red blood cells in the vessels.

Gall-bladder. Sections disclose the mucosa to be bile-stained, denuded and roughened. There is a slight thickening in the sub-mucosa. A lymphoid follicle is seen in one part of the serosa. In sections stained for bacteria a few cocci in short chains and a few diplococci are found.

Liver. The cord of liver cells stain palely and are quite shrunk so that the capillary spaces are relatively wide. Nearly all the cells but mostly those around the central veins contain fat droplets. There is much yellow pigment both intra- and extracellular. No bacteria are found in the sections.

Spleen. The Malpighian bodies are prominent. The pulp is packed with red blood cells and yellowish pigment, evidently from broken down red cells. The pulp is relatively free from lymphoid cells. The blood sinuses are definitely outlined but contain few red blood cells and many white cells.

Bone-marrow. Sections from a rib and the femur show marked cellular activity. The fatty reticulum present in the normal adult femur is replaced by active marrow elements so that the sections from the two bones are indistinguishable. The large number of megalocytes, megaloblasts and normoblasts seen among the marrow cells is striking. A differential count made of several areas to get an idea of the percentage of the different types shows approximately in each area, respectively: (a) 8 myelocytes, 10 myeloblasts, 5 normoblasts, 4 non-nucleated red blood cells; (b) 4 myeloblasts, 5 normoblasts, 4 non-nucleated red blood cells, and (c) 4 myeloblasts and myelocytes, 1 polymorphonuclear leukocyte and 4 lymphocytes.

Bacteriological. Cultures of the bile were negative for all organisms. *B. coli* was obtained from the gall-bladder wall, but this is thought to be a contamination.

Anatomical Diagnosis. Hyperplasia of the bone-marrow; generalized pallor of the skin; atrophy of gastric mucosa; multiple hemorrhages of serous membranes; chronic atrophic cholecystitis; pernicious anemia; hyperplasia of mesenteric and biliary lymph nodes; yellow atrophy and slight interstitial fibrosis and slight fatty changes of the myocardium.

CASE VI.—(Multnomah Hospital Service). W. H., aged twenty-three years, was received December 1, 1922. Patient had suffered for four years with relapsing weakness and paleness, swelling of feet, numbness of hands and feet, and periodic pain and swelling in left hypochondrium for two years. During the past summer the patient was in bed for seven months with such an attack to which a chronic dysentery was added. The present attack of pain began one week before entrance to the hospital. It was associated with chills, fever and profuse sweating. He had developed an acute gonorrheal iritis from an old urethritis, smears showing Gram-negative intracellular diplococci. He presented a general septic appearance with a profound lemon-tinted type of anemia.

The history revealed measles and jaundice in childhood, left-sided pleurisy, many attacks of sore throat and a Neisserian infection three years ago.

Examination. A pale, asthenic male, profoundly weak, severe dental infection; first heart tone, left, possesses a rumbling murmur at times—absent at other times. There is diffuse abdominal tenderness, more marked in the left hypochondrium, together with a mass felt beneath the left costal arch. The feet are edematous. The stomach chemistry is not investigated. The urine shows albumin and pus with Gram-negative diplococci and Gram-positive chained streptococci. Gall-bladder not examined. The blood Wassermann is negative and one blood culture is also negative. Six blood examinations showed hemoglobin, 68 to 58 per cent; erythrocytes, 2,944,000 to 1,896,000; leukocytes, 3000 to 4600; polymorphonuclears, 40 to 64 per cent; small mononuclears, 26 to 36 per cent; large mononuclears, 8.5 to 20 per cent; eosinophiles, 0 to 1.5 per cent; transitionals, 0 to 2.5 per cent; myelocytes, 2 to 4 per cent; nucleated red cells negative; marked changes in the size and staining of the red cells. Death, February 9, 1923.

Autopsy. This is the body of a moderately emaciated white man, aged twenty-three years, skin pale; skin about the ankles pits on pressure. Pelvis and abdominal cavities contain about 2 liters of straw-colored fluid. Liver is large. The lower pole of spleen is seen just below the costal margin in the left midclavicular line. Four septic anemic infarcts are present in the spleen. The upper

pole is adherent to the diaphragm by fibrous bands; when dissected away a well walled-off subdiaphragmatic abscess 2 x 3 x 5 cm. is found. The capsule of the spleen is tense. The cut surfaces disclose a moderate hyperplasia of the pulp and engorgement with blood. The spleen weighs 1500 gm. The gall-bladder is greatly swollen due to edema of the wall. Beneath the serosa there are numerous small hemorrhages. The sac contains viscid brownish bile. The biliary lymph nodes are hyperplastic. The main bile ducts are patent.

Each pleural cavity contains a liter of straw-colored fluid in which the lungs float. Petechial hemorrhages are abundant in the visceral pleural of each lung. The lung is densely adherent to the diaphragm. The pericardial sac is distended with straw-colored fluid. The heart is dilated and flabby; its musculature is pale. At the junctions of the leaflets of the mitral valve there is a ragged ulceration with destruction of a few of the chordæ tendineæ. The cut surfaces of the lungs reveal a passive hyperemia and atelectasis at the bases. The cut surfaces of the kidneys are dark, glomeruli red. In the liver the lobules are well outlined, parenchyma friable, and the blood which exudes is pale reddish and thin.

Microscopically the heart shows areas of focal necrosis, hyaline degeneration, and scar tissue, which has the appearance of having been recently formed, scattered throughout the myocardium.

Liver. Sections disclose a moderate atrophy of the cells, especially about the central veins, where also fatty changes and intra- and extracellular pigment is found. No bacteria in the liver. The abundance of pigment obscures the picture.

Gall-bladder. Sections reveal small hemorrhages in the serosa, marked edema of subserosa, moderate increase in fibrous connective tissue, and partial desquamation of epithelium of mucosa. A few round cells are present. Sections stained by Unna's alkaline methylene-blue method for bacteria disclose many organisms in chains that look like streptococci.

Spleen. The sinuses are filled with red blood cells and pigment containing phagocytes. There is a slight hyperplasia of the lymphoid cells. Other sections disclose septic anemic infarcts covered with fibrinous exudate.

Kidneys. There is hemorrhage, recent and old, into the subcapsular spaces of Bowman and into the convoluted and straight tubules.

Lungs. Chronic passive congestion and atelectasis.

Bone-marrow. Not examined.

Bacteriological. A pure culture of long-chained hemolytic streptococcus was obtained from the bile and the wall of the gall-bladder. Cultures from an infarct in the spleen gave the same organisms and *B. coli*. Cultures of the spleen pulp were negative. Intravenous injection of the organisms in a rabbit produced purulent arthritis

and bacteriemia in two days. The organisms were recovered from the joints and the heart blood. Cultures of the bile and gall-bladder of the animal were sterile.

Anatomical Diagnosis. Subacute ulcerative endocarditis—mitral valve; multiple septic infarcts in the spleen; small subdiaphragmatic abscess involving upper pole of spleen; focal necrosis and scarring of the myocardium; moderate atrophy; chronic and acute dilatation of all chambers of the heart; moderate ascites, bilateral hydrothorax, hydropericardium and edema of the ankles; chronic passive congestion of the liver; atrophy, fatty and pigment changes; chronic passive congestion of the lungs, atelectasis of lower lobe; subacute and chronic cholecystitis with hyperplasia of biliary lymph nodes; marked chronic anemia; moderate emaciation; chronic hyperplasia and hypertrophy of the spleen; petechial hemorrhages in visceral pleuræ and serosa of gall-bladder; hemorrhage in kidneys; fibrous pleuritis, base of left lung. Examination of bone-marrow was overlooked.

CASE VII.—(Medical Division U. S. Veterans' Bureau). F. M., male, aged forty years, was not studied during life by us but came to autopsy by Dr. Hunter, March 9, 1923. The history from the Veterans' Bureau is that of a frank pernicious anemia beginning some time previous to January, 1918, and characterized by several relapses and remissions until death occurred March 8, 1923.

Examination. The patient is emaciated; weight 114 pounds; very anemic; of sallow, brownish hue; some dental and tonsil sepsis; hemic heart murmur. The blood on several occasions showed hemoglobin, 50 to 25 per cent; erythrocytes, 1,500,000; leukocytes, 3000. The red blood cells are irregular in shape, size and staining properties. There are no nucleated red blood cells found. A blood culture is negative.

Autopsy. This is the body of a poorly nourished white man, aged forty years. There is a general brownish pigmentation of the skin.

The gall-bladder is small, thick walled and contains a single large soft bile-pigment stone. The mucosa is desquamated and denuded. The cystic, hepatic and common bile ducts are patent. The surface of the liver is finely pebbled; the parenchyma cuts with increased resistance; the blood which exudes is pale and watery.

The lungs are emphysematous. On section, small discrete consolidations are seen. In the visceral pericardium are numerous petechial hemorrhages. The heart is large, flabby and pale. The musculature, especially at the bases of the papillary muscles, is pale and fatty. The endocardium presents the mottled appearance described as "tigerling;" no valvular lesions. A number of calcified lymph nodes found at the bifurcation of the trachea. The spleen is slightly enlarged; cut surfaces reddish and moderately fibrous. The marrow of the long bones is markedly hyperplastic.

Microscopically the gall-bladder shows a greatly thickened and fibrous wall. The mucosa is desquamated and denuded except in the deeper portions of the crypts. Ulceration extending to the muscularis occurs, and in these areas polymorphonuclear leukocytes and small round cells loaded with bile pigment are numerous. Foreign body giant cells containing bile pigment are also present. Bacteria are numerous; morphologically they resemble staphylococci.

Liver. There is considerable atrophy of the hepatic cells especially about the central veins, so that the capillary spaces are widened. Intracellular pigment is abundant. In certain areas the bile capillaries are hyperplastic and newly formed capillaries are numerous. In other areas there are small focal necroses and distinct patches of scar tissue, which in some instances entirely surround islands of liver cells. In sections stained for bacteria the large amount of pigment obscures the field and no organisms are found.

Bone-marrow. Stained smears disclose well-marked poikilocytosis, anisocytosis, moderate numbers of nucleated red cells, 1 megalo-blast, and polychromatophilia.

Bacteriological Findings. Culture; not made on account of embalming.

Anatomical Diagnosis. Subacute and chronic ulcerative and endurative cholecystitis with cholelithiasis; numerous fibrous adhesions between gall-bladder and other organs; hyperplasia of bone-marrow; pernicious anemia; focal biliary cirrhosis of the liver with atrophy; fatty and pigment changes; fatty change in the myocardium—"Tiger heart;" petechial hemorrhages in pericardium; moderate emaciation; generalized brownish pigmentation of the skin; moderate atrophy of suprarenal cortex; slight fatty and myxomatous changes in the aorta; calcified tuberculous lymphadenitis; rudimentary right kidney, weight 40 gm.

CASE VIII.—(Multnomah Hospital Service). C., aged forty-seven years, was received April 8, 1923. The patient has suffered from a progressing weakness and paleness for more than eight months. Six months ago his hands became numb and soon afterward failing strength in his legs prevented his walking. On entrance he was unable to stand. For two months he has been awakened at night with indefinite pains in the region of the stomach. He thinks he was jaundiced when the pains began but he considers himself jaundiced now. He has had repeated nose bleeding and possibly two chancroid infections. He has lost much in weight.

Examination. The patient is profoundly weak and undernourished though not emaciated. The skin is pale and lemon tinted. The teeth are foul with sepsis and neglect. The tonsils are septic. The tongue is inflamed. There is some generalized lymphadenopathy. There is a discharge from the left ear. A hemic murmur is

heard over the precordium. The patient is considered too weak to make stomach analyses or to study the gall-bladder. There is some increased muscle resistance in the right upper abdominal quadrant; the reflexes are present but weak. The blood Wassermann is negative. Several blood counts show on an average: Hemoglobin, 40 per cent; erythrocytes, 1,640,000; leukocytes, 4800; polymorphonuclears, 62 per cent; small mononuclears, 22 per cent; large mononuclears, 11 per cent; eosinophiles, 1 per cent, transitionals, 1 per cent; questionable myelocytes, 3 per cent; irregular red cells and irregular staining at present. No nucleated red blood cells are found.

Death May 12, 1923.

Autopsy. This is the body of a somewhat poorly nourished white man, aged fifty-one years. The skin, particularly of the face, had a lemon-yellow tinge. The subcutaneous fat is firm and lemon-yellow. There are petechial hemorrhages in root of the mesentery and in the mucosa of sigmoid. The blood is darker red than normal. The gall-bladder is empty and collapsed; it is free from adhesions but its wall is whitish and slightly thickened. The bloodvessels are unusually prominent. It contains a very small amount of stringy brownish bile. The mucosa is intact and there are no concretions. The biliary lymph nodes are small. The larger bile ducts are unchanged. The central veins in the liver are prominent. The spleen weighs 250 gm. The cut surfaces are reddish and firm; Malpighian bodies are visible.

The rugæ of the stomach are lacking; the mucosa is atrophic. The marrow of a portion of the middle third of the tibia discloses a patchy hyperplasia of the blood-forming tissue. The marrow of the ribs is soft and hyperplastic. There are no gross lesions in the brain or spinal cord.

Microscopally the sections of the yellow marrow disclose a moderate hyperplasia of erythrogenetic islands which partially replace the fat. In these islands there are seen megaloblasts, normoblasts, poikilocytes and microcytes and also an increased number of myeloblasts and myelocytes. Phagocytes containing pigment are present. Sections of the red marrow disclose a marked hyperplasia of the blood-forming tissue.

Gall-bladder. The mucosa is intact and normal in appearance. There is a slight diffuse increase in fibrous tissue throughout the wall with scattered round cells in moderate numbers between the fibers. Sections stained for bacteria disclose bacteria for the most part in the form of diplococci.

Spleen. The Malpighian bodies are prominent. The sinuses are engorged with red blood cells in all stages of disintegration. Phagocytes containing broken red cells and pigment are numerous. All types of abnormal red cells are found.

Liver. About the central veins there is almost complete atrophy of the hepatic cells with some fatty degeneration. Phagocytes containing brownish pigment and shadows of red cells are seen in these regions. The bile capillaries are unchanged.

Stomach. The mucosa shows well marked atrophy with replacement of fibrous tissue and an infiltration of small round cells and plasma cells.

Heart blood . . .	Pneumococcus in pure culture.
Lung	Pneumococcus in pure culture.
Gallbladder . . .	Pneumococcus and alpha-hemolytic streptococcus.
Bile	Pneumococcus and alpha-hemolytic streptococcus.
Liver	Pneumococcus and Bacilli coli.
Bone-marrow . . .	Pneumococcus in pure culture.

Anatomical Diagnosis. Well marked hyperplasia of the red bone-marrow, slight hyperplasia of the yellow bone-marrow; yellowish pigmentation of the skin; petechial hemorrhages in root of mesentery and mucosa of sigmoid; atrophy of gastric mucosa; pernicious anemia; slight chronic diffuse cholecystitis, isolated streptococcus and pneumococcus; syphilitic arteriosclerosis of the aorta; old fibrocaseous tuberculosis of upper right lobe; atrophy and pigment changes in the liver; slight atrophy and fatty changes in the myocardium; moderate hypertrophy of the spleen; lobar pneumonia, lower right lobe; pneumococcus septicemia; sero-fibrino-purulent, right; purulent bronchitis; slight parenchymatous degeneration of the kidneys; interstitial orchitis and atrophy of interstitial cells.

After reviewing the data presented, Dr. Everett O. Jones (Seattle; Wash.) operated on a patient suffering from a frank pernicious anemia, who was under the care of Dr. Edward P. Fick. We are indebted to him for the records of the case, a résumé of which follows:

CASE IX.—(The Swedish Hospital, Seattle, Wash., Service of Drs. Jones and Fick). W. J. B., aged fifty-two years, ship captain, had been sick at irregular intervals for three years with weakness, paleness, anorexia, diarrhea and numbness above the left knee. One year ago the attack lasted two months. October, 1922, he was delirious for a week during an attack, after which he slowly recovered until January, 1923, when the present relapse began. The patient has used alcoholics to excess. He has spent seventeen years in the Orient and had cholera in 1893.

Examination. The patient is well nourished; the skin pale and lemon tinted; the mucous membranes pale; dental sepsis is severe. The tongue shows no atrophy or inflammation. There is a murmur over the precordium. The stomach shows complete achylia. The reflexes are normal except the knee kicks, which are sluggish. Eight blood examinations were made; one of them is herewith recorded: Hemoglobin, 15 per cent; erythrocytes, 1,200,000; leukocytes,

6000; small mononuclears, 60 per cent; large mononuclears, 40 per cent; 1 normoblast was found in the eight examinations, and the red blood cells show marked anisocytosis and polychromatophilia. The blood Wassermann was negative.

Treatment. It seemed evident that the patient would not survive this relapse, so an exploratory operation was advised and accepted. The gall-bladder was normal in appearance. It was removed and from the gall-bladder wall a pure culture of a hemolyzing *Staphylococcus albus* was obtained. The bile was sterile.

Death occurred on the day following operation.

Abstract of Autopsy Record. The autopsy was made the same day by Dr. D. H. Nickson. The general appearance of one dead of pernicious anemia is present. Multiple pin-point submucous hemorrhages in the fundus of the stomach exist. The mucosa of the pylorus and first part of the duodenum is markedly thickened and edematous, measuring $\frac{3}{8}$ cm. in thickness. The liver appears normal. The site of the operation is normal; there has been no hemorrhage. The spleen weighs 320 gm. Smears from the spleen pulp show many megalocytes and some nucleated red blood cells. The bone-marrow of the tibia is dark red, hyperemic, and sections show hyperplasia of the elements.

Comment. (N. W. J.) This patient presented during life the course of a frank pernicious anemia. Never had there been any suggestion of gall-bladder disease either before or during his final illness. At operation the gall-bladder appeared to be normal but it was removed and a hemolyzing *Staphylococcus albus* was obtained in pure culture from its wall. The patient, already approaching his end, was unable to withstand the shock of operation.

CASE X.—Mrs. D., aged sixty years, 4 para, was received March 23, 1923. Patient first noticed an oncoming anemia, weakness and loss of weight following the extraction of the teeth for dental sepsis one year ago. These symptoms together with nausea, vomiting, dyspnea, pains in the chest and arms and a recurring soreness of the tongue have been more marked during the last four months. Her past history has been negative.

Examination. The skin is pale and lemon tinted; the mucous membranes are pale; the tongue shows a bright red inflammation about the tip and the dorsum is glossy and fissured. The tonsils are septic. A hemic murmur is heard over the precordium. The stomach shows complete achylia. The stools are negative. The blood Wassermann is negative. Thirteen blood counts were made during the five weeks the patient was in hospital under treatment. The first blood count showed: Hemoglobin, 50 per cent; erythrocytes, 1,990,000; leukocytes, 4200; polymorphonuclears, 57 per cent; small mononuclears, 38 per cent; large mononuclears, 2 per cent;

eosinophiles, 1 per cent; normoblasts, 1; megaloblasts, 2; marked anisocytosis and polychromatophilia. The last blood count showed: Hemoglobin, 75 per cent; erythrocytes, 3,470,000; leukocytes, 3400; polymorphonuclears, 70 per cent; small mononuclears, 28 per cent; large mononuclears, 2 per cent; basophiles, 1 per cent; eosinophiles, 1 per cent; no nucleated red blood cells, and less marked changes in the size and staining of the erythrocytes.

Faint but positive shadows of the gall-bladder were obtained April 30, 1923. There was no distortion or spasm of the duodenum. Operation was performed May 28, 1923. A chronically infected gall-bladder and appendix were removed (by T. M. J.). A small bit of liver was removed for examination.

Pathological Report. The gall-bladder wall is moderately thickened. There is a small amount of viscid bile in the sac. The gall-bladder is partially necrotic (due to delayed examination). Necrosis is too marked for accurate histological study. The wall appears thickened and fibrous. The mucosa is desquamated and the cellular outline is indistinct. Sections stained for bacteria are negative, probably due to autolysis. Sections of the liver show slight necrosis of the cells. Some contain granular brownish pigment. The walls of the capillaries are thickened, due to increase in fibrous tissue in which a few small round cells are present. The epithelium is intact. Sections stained for bacteria show no organisms. Cultures of the bile and gall-bladder are negative. Cultures of the liver show a prolific growth of green producing alpha-hemolytic streptococcus.

Pathological Diagnosis. Chronic cholecystitis and chronic cholangitis.

Course. Convalescence from operation was prompt. The rapid change in symptoms and general appearance noted in the other patients operated upon was observed again. The skin lost its lemon color and became pink. The patient's general sense of feeling became different. (This change has been noted and commented upon by the other patients operated upon.) A very sore glossitic tongue became symptomless within three days. The soreness of the tongue returned, however, after three weeks and still bothers somewhat. The blood before operation showed: Hemoglobin, 75 per cent; erythrocytes, 3,440,000; leukocytes, 5700; moderate changes in size and staining properties of the red cells. On leaving the hospital it showed: Hemoglobin, 85 per cent; erythrocytes, 3,390,000; leukocytes, 5600, and less marked changes in the red cells. And the last examination, August 4, 1923, was: Hemoglobin, 78 per cent; erythrocytes, 2,580,000; leukocytes, 4650, and more marked changes in the red cells.

Comment. This patient represents the type of pernicious anemia characterized by a rapid downward course, with few or no remissions and with many megaloblastic cells in the blood stream.

The same clinical betterment has been noted as in the other patients operated upon and this improvement seems out of proportion to the changes which have taken place thus far in the blood cells. Nevertheless, it is so noticeable to the patient herself that she believes she is going to become well. She bases this upon her increased strength, the fact that she is able to walk up short hills and stairs without shortness of breath and undue fatigue, and that her general sense of well-being has been markedly changed. Although only two months have elapsed since operation and one is not justified to form any conclusions regarding the outcome, still we recognize in this instance, as in the others, a more profound change than we have ever noted in any other form of treatment employed, including splenectomy. Whether the cause of the anemia has been removed or not, nevertheless, the effect thus far seen justifies the hope that some definite modification of the disease has taken place. The streptococcus obtained from the liver tissue undoubtedly existed in the wall of the gall-bladder also.

The brief records of the following 3 patients are also included for the reason that all of them have shown roentgenological evidence of gall-bladder disease. No thought of the existence of such disease would have been seriously considered in 3 of them. In 1 patient recurring attacks of pain and a possible attack of jaundice might have caused the association of gall stones and the anemia to be considered.

CASE XI.—Mrs. L., aged fifty-one years, 6 para, was received for the first time October 17, 1914. She had suffered all her life from gastro-intestinal disturbances, vomiting, periods of bowel looseness, fever lasting at times for months, and in later years relapsing periods of paleness and weakness. She had had jaundice in childhood, and tonsil, sinus and dental sepsis for many years. At one time pain in the lower right abdomen led to the diagnosis of chronic appendicitis but she was not operated upon. Later she suffered pain attacks in the left chest. The heart was normal in all examinations except for hemic murmurs heard during relapses. For some years she suffered from numbness, burning and tingling of the hands and feet and of the tongue. Between October, 1914, and June, 1922, the patient was in our care eight times for longer or shorter periods of observation. She suffered from a complete achylia and a severe secondary bowel disturbance. Twenty-three complete counts were made. The persistent characters of pernicious anemia were always present. Nucleated red blood cells were never found. Positive shadows of a diseased gall-bladder with the presence of stones were obtained June 5, 1922. Cholecystectomy was urged at that time as a possible relief for the anemia but was not accepted.

Death occurred during a relapse at her home in an adjoining state, in March, 1923.

CASE XII.—Mrs. McP., aged forty years, 1 para, was seen June 20, 1922. Patient had complained for a year of exhaustion. Constipation had existed for fifteen years and the skin had been sallow for a long time. Once for a short time; one year ago, and lately for six weeks, patient has had some dull distress in right upper abdomen. She has had a dental sepsis. The tongue is negative; the stomach shows complete achylia. There are no paresthesiæ. Two blood examinations show: Hemoglobin, 90 per cent; red blood cells, 3,400,000; white blood cells, 5000. The red blood cells show a moderate number of megaloblasts and some polychromatophilic staining. There are no nucleated red blood cells. The blood Wassermann is negative. Positive gall-bladder shadows, without evidence of stones, are obtained on the films. Operation is not accepted.

CASE XIII.—Mrs. E., aged sixty-three years, 6 para, was received March 22, 1923. Since an acute illness two years ago the patient has been developing an increasing weakness and paleness; constipation exists but no bowel looseness. Soreness and burning of the tongue have been present for the last two weeks. Parasthesiæ have been absent. There is an old history of dental sepsis. The patient has a marked lemon-tinted paleness of the skin, glossitis, complete achylia and a megaloblastic blood picture. Positive gall-bladder shadows with stones are obtained. On entrance to hospital the blood examination showed: Hemoglobin, 42 per cent; erythrocytes, 1,680,000; leukocytes, 3200 and numerous normoblasts and megaloblasts. She remained one month under treatment in preparation for a cholecystectomy but finally refused operation. On leaving her blood showed: Hemoglobin, 70 per cent; erythrocytes, 2,500,000; leukocytes, 3400; 1 normoblast, fewer macrocytes and no megaloblasts.

Discussion. In the accounts of the 13 cases there is presented certain clinical, operative and postmortem evidence pointing to the fact that idiopathic pernicious anemia is related to and possibly caused by the action of hemolytic or other microorganisms which have invaded the wall of the gall-bladder and from this organ as a focal site are producing their effect upon the red blood cells and erythrogenetic centers of the bone-marrow. In the 10 operated or autopsied cases the wall of the gall-bladder afforded organisms by culture or by staining the tissues, or by both methods. In the 7 instances in which cultures were obtained hemolyzing organisms were found in 4, alpha-hemolytic streptococcus in 2 and non-hemolytic *Staphylococcus albus* in 1. In Cases III and IX hemo-

lytic *Staphylococcus albus* was obtained and in each instance it was believed to be a pathogenic organism and not one of contamination. Case IX is of special note for the pathological and bacteriological examination was made by other observers and in-so-far as one case may decide it serves as confirmation of our own observations. Case VIII is also of special interest because in the presence of a terminal pneumococcic septicemia; an alpha-hemolytic streptococcus was obtained locally from the gall-bladder wall. The organisms lie most abundantly in the areas of scar tissue within the muscularis where possibly a lowered oxygen tension permits of a better growth. In this respect it reminds one of the localization of *Streptococcus viridans* in the leaflets of the heart valves in subacute infectious endocarditis. It raises the query whether or not the organisms may be able to seal themselves up within a suitable medium that permits growth over a long period of time and thus allows an organism of low virulence to produce death of the host after many months or years, even as the *Streptococcus viridans* does in the heart. In Cases IV and X a bit of liver tissue gave a pure culture of alpha-hemolytic streptococcus. In none of the autopsied cases have organisms been thus obtained. They also have not been found in sections of the liver stained for bacteria, but the presence of pigment obscures the picture. Whether these organisms will be universally found in the liver substance, as Graham¹⁷ has shown in ordinary cholecystitis, remains to be determined.

The macroscopical appearance of the gall-bladder is important. In Cases III and IX it was considered normal by the surgeon. In Cases II, IV, V, VIII and X the macroscopical evidence of disease was slight. In Case VI an unsuspected gall stone was found at autopsy. In all cases studied roentgenologically by Dr. Palmer for the presence of chronic gall-bladder disease sufficient proof was found to justify the removal of the organ. This emphasizes again the contention that positive gall-bladder shadows are more conclusive of disease than the macroscopical appearance of the gall-bladder at operation. In only 1 case of the series (Case I) was there sufficient clinical evidence to justify the thought that chronic gall-bladder disease might be present.

From the therapeutic standpoint there is much to be learned that only the experience which comes with time will teach. If these observations are proven to be true in a reasonable percentage of cases, it would seem justifiable to perform cholecystectomy in those instances, at least, in which roentgen-ray evidence of gall-bladder disease is obtained. Indeed, if suitable roentgen-ray studies are not available, it might still be proper to remove the gall-bladder inasmuch as we are dealing with an incurable disease. With a record of only 5 operated patients but little may be said. One patient has lived for six years after operation with apparent abeyance of those

symptoms of pernicious anemia from which she suffered at the time of operation. The second patient was suffering from a severe and frank although slowly progressing pernicious anemia. The result of operation in his case after eleven months' time is certainly all that could be hoped for. One must not wait for the appearance of megaloblastic cells in the blood stream or the presence of cord changes before thinking of pernicious anemia. If the disease is caused by various organisms of special characters and of different degrees of virulence the variations in its clinical course are easily understood, and the earlier treatment is instituted the more perfect may be the end-result obtained. A case in point is the following: A strongly built woman, aged fifty-seven years, began in November, 1922, to have nausea and vomiting. Two months ago an annoying flowing of saliva and a distressing soreness of the mouth began, which were laid to the door of septic teeth and tonsils. These were removed. About the same time one hand became numb. A recent examination of the patient did not reveal any local cause of the salivary disturbance within the head. The chemistry of the stomach was normal. The blood examination showed hemoglobin 100 per cent and red blood cells 4,900,000. There were some macrocytes present. Positive proof of a gall-bladder disease was obtained. With this combination of subjective symptoms and gall-bladder disease a beginning pernicious anemia may well be considered *

One more point in regard to the treatment of these cases may be mentioned. For over twenty years large doses of arsenic, especially of sodium cacodylate, have been empirically used with benefit in the treatment of streptococcic infections. For a much longer time arsenic has been the most efficient means employed in prolonging the life and alleviating the suffering of the patient with pernicious anemia. The underlying reason may be the same because of the inhibiting power which arsenic has on these organisms. We have safeguarded our operative results by treating the patient in bed with arsenic to the point of physiological tolerance, forced feeding and hydrochloric acid. With each patient we have aimed to raise the hemoglobin content above 70 per cent, the red cell count to 3,000,000 and to add several pounds to the weight before operating, and then to operate before the beginning of another relapse. The 1

* Cholecystectomy and appendectomy was performed on this patient June 14 (by E. W. St. P.). The pathological report is as follows: The gall-bladder wall is slightly thinned, the mucosa atrophic sections show thinning of the wall, slight fibrosis of the muscularis, atrophy and desquamation of the epithelium of the mucosa. In the wall are some large lymphocytes and small round cells. Sections stained for bacteria show the presence of a few diplococci and intracellular cocci. The bit of liver tissue is not sectioned. Cultures of the bile, the gallbladder and the liver are negative.

Pathological Diagnosis. Chronic atrophic cholecystitis. *Course.* Convalescence from the operation was normal. The drooling and the numbness of the hand practically disappeared before the patient left the hospital.

death recorded occurred in the wake of a relapse. It is not unlikely that an exaggerated risk may be present at this time, although the experience of splenectomizing such patients does not wholly bear out this view.

Experimental work has been started in the pathological laboratory in an effort to determine whether some of the organisms isolated from the gall-bladders of pernicious anemia patients are pathogenic for animals. It is the purpose also to determine if possible whether pernicious anemia is caused directly by the lytic action of bacteria and their products on erythrocytes, or whether the anemia may be the effect of some chemical substance entering the circulation from the infected gall-bladder. The fact that the lytic substances causing the pernicious anemias of *Bothriocephalus latus* and of hookworm infections are lipid in character, and that a megaloblastic anemia may be produced experimentally in rabbits by using a similar agent, suggests the possible changes in the cholesterol content of the bile, especially within the gall-bladder, by means of organisms possessing special properties as being the cause of another group. These studies will be reported later.

Conclusions. 1. Evidence is brought forth pointing to the presence of hemolyzing and other microorganisms in the wall of the gall-bladder as being the possible cause of idiopathic progressive pernicious anemia.

2. In a series of 13 cases the presence of chronic gall-bladder disease was found by special study in each one.

3. Cholecystectomy on 5 patients of this series seemingly has removed some or all of the symptoms of the disease.

BIBLIOGRAPHY.

1. Addison: Idiopathic Anemia: On the Constitutional and Local Effects of Diseases of the Suprarenal Capsules, London, 1855.
2. Biermer: Cor.-bl. f. schweiz. Aertze, 1872.
3. Hunter: Brit. Med. Jour., March 18, 1922, 421.
4. Schaumann and Tallqvist: Deutsch. med. Wehnschr., 1898, 24, 312.
5. Schaumann: Akademische Abhandlung, Helsingfors, Weilin and Goos, 1894, p. 214.
6. Faust and Tallqvist: Arch. f. exp. Path. u. Pharmacol., 1907, 57, 367.
7. Ashford and King: Jour. Am. Med. Assn., 1907, 49, 471.
8. Whipple: Jour. Exp. Med., 1909, 11, 333.
9. Bunting: Johns Hopkins Hosp. Bull., 1900, 16, 222; Jour. Exp. Med., 1907, 8, 625; Jour. Am. Med. Assn., 1907, 49, 476.
10. Madler: Jour. Med. Res., 1913, 28, 199.
11. Eppinger: Berl. klin. Wehnschr., 1913, p. 1553; 1913, p. 2409.
12. v. DeCastello: Wien. klin. Wehnschr., 1913, 26, 951.
13. Georgi: Berl. klin. Wehnschr., 1887, p. 822.
14. Ewald: Berl. klin. Wehnschr., 1887, p. 850.
15. Percy: Surg., Gynec. and Obst., 1917, 24, 533.
16. Giffin and Bowler: Minnesota Med., 1923, 6, 14.
17. Graham: Surg., Gynec. and Obst., 1918, 26. Graham and Peterman: Arch. Surg., 1922, 4, 23. Peterman, Priest and Graham: Arch. Surg., 1921, 2, 92.

DIABETES SURGERY.

BY M. G. SEELIG, M.D.,

ST. LOUIS, MO.

(From the Surgical Service of the Jewish Hospital of St. Louis.)

FEW diseases require a closer coöperation between surgeon and internist than does diabetes. The type of coöperation called for demands on the part of the surgeon, at least a fairly comprehensive knowledge of the work that has been done and is being done, in metabolism studies of blood and urine; and on the part of the internist, an appreciation of the refined judgments of the surgeon, attempting to determine whether or not a patient with a simple uncomplicated diabetes should be subjected to operation for a lesion unrelated to his glycosuria; or whether a diabetic patient with a surgical complication is able to withstand the life-threatening dangers incident to operative interference.

In the instance of diabetes, as in the case of quite a large number of diseases that may require surgical treatment, the facts of most fundamental importance have been developed by internist, physiologist, pathologist, and chemist. It would seem almost to be an affront for a surgeon to emerge from within his charmed circle of pure technic. The fact of the matter, however, is that the real surgeon strives most zealously to comprehend, to appropriate and to apply properly the principles discovered by his colleagues in other branches. In this process of comprehension, appropriation and application, it not uncommonly happens that the humble surgeon contributes his mite, both to science and to suffering humanity.

Twenty years ago, the problem of surgery on diabetics was a fairly simple one. It was then generally conceded that the dreaded postoperative coma could be best averted by a fairly liberal carbohydrate intake just before, and as soon after operation as possible. Diabetes was, of course regarded as a possible *nolle me tangere*, and consequently, operative indications were set prayerfully, and with due consideration; but the chemistry involved in acidosis, the question of the combining power of the blood for CO_2 , the problems of the chemistry of blood sugar, and of the influence of the fat solvent power of ether as a prime factor in the production of coma, all these problems were just beginning to be linked to clinical medicine. Twenty years ago, the American surgeon operated upon a diabetic patient reluctantly, placed much faith in the use of carbohydrate feeding, and then awaited the outcome with the spirit of a hopeful fatalist who had at his command at least one powerful aid—asepsis.

In 1913, Kaposi published a very exhaustive clinical and bibliographical study of surgery in diabetes. He was able to collect

less than one hundred titles covering a period of the preceding twenty-five years. This is a fairly safe index of the dearth of knowledge of the subject, up to ten years ago; for there is a great tendency to appear in print, on the part of those of us who only presume that we have something worthwhile to say. Even in this scanty literature, there were many conflicts. For example, one surgeon, Sternberg, said that any necessary operation may be performed with safety, on a diabetic. Other surgeons (Lepine and also Kausch) said that every operation is contraindicated in diabetes. Da Costa said that the increased sugar content of the blood made it a favorable culture medium, and that operation wounds in diabetics were therefore frequently infected. Handman, on the other hand, explicitly refuted this statement, and showed that the growth of staphylococci was the same in diabetic as in non-diabetic blood, that the bactericidal power of blood is not influenced by the addition of 1 per cent of sugar, and that its opsonic index likewise, is not influenced. Surgeons in general, had a wholesome fear of postoperative coma in any diabetic patient; and yet, Manges concluded that, "The surgeon has too much fear of acidosis. There is no danger, no matter how intense the acetone reaction may be, when the diacetic acid or the oxybutyric acid tests are negative."

From conflicting opinions such as these, it is not warrantable to draw the conclusion that fifteen or twenty years ago, the problem of surgery in diabetes was in a state of chaos. Certain principles governed the thoughtful surgeon—principles that maintain even today, except for those modifications that have resulted from the introduction of insulin. In the first place, it was recognized that diabetes was a disease varying in severity from the mild to the severe, and that the results of surgical interference were measurably proportionate to the grade of the disease. It was regarded as true von Noorden's axiom that: Every diabetic is, emphatically, less resistant to trauma (including surgical trauma) than is a non-diabetic patient. It was known that anesthesia was a precipitant factor in the production of coma, that wound healing was proudly affected by a high blood-sugar content, that wound infection was to be feared, and that immunity to infection in general was low in diabetes. Finally, and most important of all, it was known that not only were special tissues compromised, but also, that the organism as a whole was weakened by diabetes. The frequency of endarteritis, myocarditis and neurotrophical disturbances, the not uncommon loss of weight, and the frequent existence of nephritis were facts of common knowledge to the surgeon. They counted much more with him than did academic discussions as to the whys and wherefores of their existence.

During the past ten years a voluminous amount of work has been done on the very fundamental problems of blood-sugar and blood-fat content, on ketonuria, on the CO_2 combining power of the blood,

on the reactions of renal epithelium to blood sugar, on the broad general problem of carbohydrate metabolism in its relation to diabetes. Although this work has not appreciably altered the practical relationships between surgery and diabetes, it is nevertheless necessary for the surgeon to be in possession of the new fundamental facts, if he hopes to set surgical indications correctly.

He must know that in the fasting normal individual, the blood contains 0.1 per cent of sugar. It is much more important for him to know that this is not a fixed percentage. A perfectly normal individual may have as much as 0.16 per cent, or even a somewhat higher percentage. Hamman and Hirschman believe that the renal threshold for sugar is 0.17 per cent to 0.18 per cent of blood sugar. When the percentage of blood sugar rises above the normal limit, the sugar passes through the kidney and appears in the urine. That point of concentration of blood sugar at which the first trace escapes through the renal epithelium, and appears in the urine, is known as the "kidney threshold." The process of escape has been referred to as "renal leak." Both these phrases, though connotative of a purely mechanical process, are, in reality, not intended to convey the idea that the kidney is a mechanical filter. The process is, in some respects, analogous to that of filtration but an exact explanation of just how it occurs has never been furnished.

When a patient has a definitely normal percentage of blood sugar and nevertheless shows sugar in his urine, we are inclined to class him among the cases of so-called renal diabetes, and to consider him as a subject whose renal epithelium is, for some reason or another abnormally permeable to sugar. It is questionable whether this group of patients are unqualifiedly better operative risks than are those individuals suffering from essential diabetes.

There is another group, in which almost the opposite condition exists, that is, an abnormally high blood sugar, with no sugar in the urine. From the point of view of surgical disaster, this last mentioned group is menacing. Not infrequently these patients give a history of having been rather casually and yet, seemingly successfully treated for diabetes. Frequently, the story is that, some time in the past, they took one or more cures at Carlsbad, and have shown little or no sugar, since the last treatment, a year or more in the past. Urinary examination confirms the absence of sugar, the patient seems to be a good operative risk, but nevertheless, operation is followed by coma. Two years ago, just such a patient of mine, after a simple colostomy for cancer, was rescued from profound coma by persistent and rather heroic intravenous administration of dextrose. The colostomy was done under local anesthesia. This particular patient, in common with most of the patients in this group, had nephritis of mild grade. It is commonly assumed that a nephritis tends to raise the renal threshold of sugar, so that as the nephritis manifests itself more and more, the glyco-

suria becomes less and less pronounced. Mosenthal contests this view however, and says that the threshold for sugar is raised by many factors other than nephritis, and that in some instances, nephritis is accompanied by a distinct lowering of the kidney threshold.

Whether nephritis, raises, lowers or does not influence the kidney threshold, is not in itself, of vital importance to the surgeon. On the other hand, it is vitally important for the surgeon to recognize the three facts that:

1. The blood sugar may be within normal limits, and be accompanied or unaccompanied by glycosuria.
2. The blood sugar may be abnormally high, and be accompanied or unaccompanied by glycosuria.
3. The blood sugar may be abnormally low, and be accompanied or unaccompanied by glycosuria.

I say that a knowledge of these facts is of importance to the surgeon, because they prompt him to ask, "If high blood sugar does or does not produce sugar in the urine, and if likewise, low and normal percentages of blood sugar does or does not produce sugar in the urine. Just what shall we consider diabetes to be?"

We have the right to ask this question, but I doubt if there is warrant to hope for a categorical answer. My very worthy, competent and in some instances, authoritative internist friends, very properly refuse to commit themselves, when I ask for a definite opinion as to the operative risk in the instance of a surgical patient with 0.2 per cent of blood sugar, and no sugar in the urine. For myself, I believe that we surgeons should consider such patients as not merely possible, or as potential, but as real diabetics; and that we should set both our operative indications and our postoperative treatment accordingly. It is necessary for us to remember that glycosuria, as a symptom, is of importance in that it is an indicator of hyperglycemia. Hyperglycemia is the root of all evil in diabetes, and however unwilling we may be to dogmatize in figures, we cannot go wrong, if we decide to regard as diabetics, all individuals whose blood sugar is 0.2 per cent, on ordinary diet, and 0.16 fasting, even though the urine contain no sugar.

Considering the above fundamental fact as established, we may next consider the purely surgical aspects of diabetes. Such a consideration will be simplified by grouping the surgical patients under the following three heads:

1. Those whose diabetes is merely an incident of seemingly lesser importance, and who seek advice regarding the performance of an operation for the relief of an unrelated condition, such as hernia, uterine fibroids, cholelithiasis, hypertrophied prostate, or less grave lesions.
2. Those who suffer from gangrene, either of the extremities or elsewhere.

3. Those who suffer from surgical infection, such as surface infections (carbuncle, furuncle, cellulitis) or from visceral suppuration of a grave nature (appendicitis, lung abscess, strangulated hernia, or any type of intra-abdominal suppuration).

Although insulin has been used for only a comparatively short time, the conclusions seem warrantable that this drug fairly guarantees against the development of coma, aids much in raising the natural resistance against infection, and probably, insures better wound healing. According to Foster, a fatal result inevitably follows major operations performed on patients whose blood sugar is over 0.35 per cent, or whose blood CO_2 combining power is less than 40 per cent. Insulin corrects both of these complications, and in so doing, has conferred probably its greatest boon on surgery. For years, surgeons have experienced the mingled sensations of hopeful expectancy and timid apprehension, hopefully expectant that some such substance as insulin would be discovered, and apprehensive that it might not be in his day.

Conceding, without qualification, the indispensability of insulin to the surgeon, the important fact remains, that before a judgment may be reached regarding the surgical treatment of a diabetic, it must be borne in mind that diabetes is a constitutional disease, affecting not only special tissues, but also the body as a whole; that this compromise of the body manifests itself by a lowered resistance against infection and trauma, by a consequently unpredictable course of wound healing, by an extraordinary incidence of undesirable postanesthetic sequellæ, such as acidosis, coma, pneumonia, and finally, by an increased incidence of undesirable postoperative sequelæ, such as thrombosis, embolism, cardiac failure and grave asthenia.

Even insulin does not furnish an escape from these facts, facts emphasizing the special surgical hazards to which diabetics are exposed. -Those patients whom we have placed in Group 1, the ones with hernia, fibroids, or other lesions unrelated to diabetes, should be subjected to operation, only when good judgment measures the disability or danger incident to the surgical disease, as greater than the risk of operating upon a diabetic. This statement affords, of course, a wide latitude of opinion; but it nevertheless stresses the fact that these patients, in Group 1, are poorer surgical risks because they are diabetics.

The patients in Group 2, those with gangrene, constitute a very distinct set. The gangrene most commonly affects the lower extremities, and is always referable to a lessened blood supply, secondary to arteriosclerosis, with endarteritis, and not infrequently, with embolus or thrombus formation. The exact role that the diabetes plays, in the production of the vascular changes is still more or less problematical, though there seems to be a direct causal relationship between diabetes and arteriosclerosis. The most strik-

ing, and one of the most important facts in connection with these peripheral gangrenes, is the marked disproportion that exists, so frequently, between the slight extent of the gangrene, and the marked degree of involvement of the vessels of the leg. I have repeatedly seen a gangrenous area only a half a square centimeter in area, at the end of a toe, accompanied by an almost incredible degree of thickening and calcification of the arteries of the thigh and leg, from Hunter's canal downward. This state of affairs occurs in the non-diabetic, as well as in the diabetic gangrenes. Equally striking is the frequency with which these seemingly insignificant gangrenous lesions occur in legs, in which the popliteal artery is completely thrombosed at its bifurcation. In an extremity of this sort, amputation below the site of vascular obstruction is generally not only useless, but is frequently hazardous, on account of the subsequent gangrene of the stump.

Peripheral gangrene of the extremity usually calls for amputation and the amputation must usually be done in the supra-condylar region, or higher. It is possible that a fortuitous circulation may permit more conservative treatment. In some instances, a definite line of demarcation forms at the base of a toe, and is followed by the spontaneous sloughing of the toe, and subsequent healing. I have seen this outcome in diabetic gangrene only once and I have seen it very seldom in arteriosclerotic gangrene of the non-diabetic variety. Good fortune has rarely smiled on my efforts to proceed conservatively with diabetic gangrene of the extremities. One should not oppose conservative methods, in any case where they offer hope; but one should be careful lest false hope handicap the patient with the dangers incident to delay. In those cases, where the gangrene is overshadowed by a complicating cellulitis and lymphangitis, it is almost always wise to devote a rational amount of time to an attempt to cure the infection, or at least to check its spread, before amputating. Such time is not wasted, for the interval may be used in regulating the carbohydrate metabolism with insulin, diet and other corrective methods.

The gangrenes other than those that occur in the extremities, are practically always due to trauma, to infection, or to both of these factors. Such a spreading gangrene of skin and soft parts, may originate in an innocent pimple, or after a hypodermatic injection or an insect sting, or after a more serious contusing trauma. For this type of gangrene, there is little to do, except to practise conservative methods. If a line of demarcation forms, excision is usually not necessary; and if a line of demarcation does not form, the surgeon cannot know where to anticipate it. In such cases, as in every instance of surgery on a diabetic, the fundamental indication for insulin and dietary regulation must be met.

Finally we come to Group 3, those patients suffering with carbuncle, furuncle, cellulitis, or visceral suppuration. Practically all

of these patients require more or less operative surgery, preceded, in some instances by such conservative measures as rest, suitable posture, and warm moist packs. From the practical surgical point of view, it makes little difference whether the infection is the result of hyperglycemia, or of lowered tissue resistance; because insulin plus dietary measures corrects both these abnormalities, and markedly increases the patient's chances to withstand infection and surgical trauma.

Nothing said at this time, regarding the preoperative preparation, and the postoperative care of diabetic patients may be regarded as final, because we are still in process of feeling our way with insulin. The procedure that I am now using, varies somewhat with the degree of urgency of the operative indication, and is largely patterned after the ideas of Joslin.

If operation may be deferred a few days, and the patient shows marked glycosuria, ketonuria, and hyperglycemia, he is immediately put on a diet moderately reduced in carbohydrates and proteins, and markedly reduced in fats. Insulin is immediately started, with one unit before the first meal, two units before the second meal, and so on, until five units are given three times daily, before meals. The urine is examined two hours after each meal. The diet is reduced daily, the fats being cut out entirely, very early in the reduction. At that point where the sugar disappears from the urine, further dietary reduction ceases, and the patient continues to receive five units of insulin, three times a day. Gradually the diet is increased, until the full caloric needs of the body are met, provided the urine remains sugar and ketone free. If sugar appears before the body's caloric needs can be met, and if it cannot be eliminated by reducing the carbohydrate, and increasing the protein and fat intake, then one unit of insulin is given for every one and a half grams or total sugar output in the urine. If the ketone bodies alone appear in the urine, then the protein and fat intake is lowered, and the carbohydrate and insulin administration allowed to remain stationary; or, the protein and fat intake remain stationary and the carbohydrate and insulin administration is increased. On the morning of the operation, the patient is given 60 gm. of glucose and at the same time enough insulin to oxidize this amount of glucose, that is, one unit of insulin for every one and a half units of glucose.

If operative interference is imperatively urgent, the patient is given 60 gm. of glucose and at the same time an oxidizing dose of insulin, and then the operation is performed. Coma is avoided by the active oxidation of carbohydrates (not necessarily the patient's own carbohydrates) and the rationale of the joint administrations of glucose and insulin lies in the fact that active oxidation is assured and at the same time enough carbohydrate is administered to protect against a possibly dangerous hypoglycemia.

Summary. The results of proper treatment are usually threefold: (1) A drop in blood sugar; (2) a drop in ketone bodies, or a disappearance of them; (3) an increase in the alkali reserve, with consequent increased combining power of the blood for CO_2 . These highly desirable results may be counted upon with more certainty, if the condition of the patient permits a six-hour delay in operating, so that the glucose and insulin administration may be repeated.¹

THE CLINICAL UTILIZATION OF LEUKOCYTE COUNTS WITH SPECIAL REFERENCE TO THE USE OF GRAPHIC REPORTS.

By ROBERT A. KILDUFFE, A.B., A.M., M.D.

LOS ANGELES, CAL.

THE first enumeration of the cellular elements of the blood, according to Gray,¹ was made in 1851. Since that time methods have been so perfected, and the results so well evaluated that blood counts are almost the most frequently utilized of all clinical laboratory procedures. In spite, however, of the extensive literature which has accumulated concerning the cytological blood examinations and the significance of the normal and abnormal variations thus demonstrated; in spite of the volumes which have been written upon the interpretation and significance of the findings thus obtained, there are times when it seems as if the resulting data do not attain their full clinical utilization.

Laboratory requisitions for blood counts are, as a rule, concerned merely with a tabulation of the numerical findings; particularly is this the case with the total and differential counts of the white cells; the degree to which these figures are correlated with the clinical data and utilized as a diagnostic and prognostic aid being directly proportionate to the acumen, experience, and reading of the clinician to whom they are reported. The purpose of the present communication is to call attention to some of the methods of graphically correlating the data obtained by white blood cell counts with the clinical data and to emphasize the clinical value of such reports.

It is a matter of common knowledge that in the majority of acute infections the severity of the process is indicated to a greater or lesser degree by the percentage of the polymorphonuclear leukocytes, while the total white cell count may be taken as a fairly accurate

¹ I am indebted to Dr. Albert E. Taussig, Chief of the Medical Service, and to Dr. C. M. Wilhelmj, for their coöperation in working out this problem of pre-operative preparation.

¹ Cell-counting Technic: A Study in Priority, AM. JOUR. MED. SCI., 1921, 162, 595.

index of the ability of the patient to combat the infection; and while these statements are in large measure true and the inferences to be drawn from them may be largely relied upon, a blind reliance upon such deductions cannot be countenanced. Alterations in the total and percentage number of the white blood cells as a response to infections are dependent upon: (1) The stimulus arising from the infection, and (2) the ability of the patient to respond to stimuli. Undue importance, therefore, cannot be placed upon one method of enumeration to the exclusion of the other; while both the total and differential counts are individually informative, the sum total of the information obtained from both together is vastly greater than that obtainable from either alone. If, for one reason or another, a choice must be made, the taking of a smear for a differential count is to be preferred as giving the greater information and, in addition, permitting of some study of the morphology and characteristics of the erythrocytes.

Leukocytosis. The majority of observers place the normal total white cell count as between 7000 and 10,000 per c.mm. and any increase beyond these figures is looked upon as a variation from the normal, and constituting a leukocytosis without, however, such variation being necessarily of pathological origin.

There are numerous factors capable of causing variations in the total white cell count, some dependent upon technical details, others of so-called "physiological" origin, and, finally, those having a pathological basis.

Among the technical factors, which must be especially guarded against by those making such examinations infrequently, may be noted: (1) Dilution of the blood by undue squeezing of the part from which the specimen is taken; (2) concentration of the blood by undue and unduly prolonged constriction of the part; (3) failure properly to mix the blood and the diluent before making the count.

Among the factors of physiological origin are:

1. Digestive leukocytosis, by which is meant the increase in the total number of leukocytes following the ingestion of food. This, at times, may be quite marked, but as a rule the counts are in the neighborhood of 10,000 to 12,00 per c.mm. This type of leukocytosis usually comes on within an hour after the ingestion of food and may extend over a period of three to five hours.² While the increase is mainly of polymorphonuclear cells, there is also an increase in the absolute number of small mononuclear cells. It has been shown that the degree of digestive leukocytosis is influenced by the amount of protein ingested, vegetables and fat having a much less marked effect. Owing to the marked fluctuation in this type of leukocytosis it has been suggested—and with reason—by Mauriac and

² Webster, R. W.: *Diagnostic Methods*, seventh edition, Philadelphia, P. Blakiston's Son & Co., p. 608.

Cabouat³ that it should be called digestive leukocytic fluctuation rather than digestive leukocytosis. This normal occurrence is the starting point for the *crise hemoclasique* of Widal to which reference will be made later. Just as under other circumstances, the leukocytic response to digestive activities may be more marked in children than in adults.

2. For reasons as yet not quite clear, pregnancy may be associated with increases in the total white cell count, sometimes reaching as high as 15,000 per c.mm.

3. A leukocytosis of from 15,000 to 20,000 per c.mm. may be found in the newborn due to a combination of factors, in which rapid blood formation and the influence of feeding are the most prominent. It is to be remembered that children are apt to show a more marked leukocytic response to stimuli than adults and that especially the percentage of small mononuclear cells seems to be more easily influenced in children.

4. Drugs, exercise and cold baths may also be responsible for an increase in the white cell count which, however, is transient in character.

Among the drugs responsible for increased leukocyte counts may be noted, quinin, camphor, turpentine, drugs of counterirritant properties, tuberculin, potassium chlorate, and thyroid extract.

In the consideration of leukocyte counts it is important to bear in mind:

1. A single count represents merely the condition at the time the count was made. The greatest value is obtained from the composite picture of several successive counts made at intervals of not less than two hours.

2. An increasing or sustained leukocytosis is of more diagnostic and prognostic value than the findings of an isolated examination.

3. The degree of leukocytosis is related as much to the ability of the patient to react as to the stimuli applied.

4. The presence of persistent leukocytosis is against the benignity of any tumor and a steadily increasing leukocytosis in malignant disease is significant of rapid growth or metastasis.

Daland,⁴ after a study of 100 normal individuals and 100 cases of the condition in question, concludes that a lymphocytosis may be taken as a diagnostic sign of chronic periapical dental infection in adults, especially when this occurs in the presence of a coincident leukopenia.

The association of a leukocytosis with internal hemorrhage has again been emphasized very recently.⁵ The factors responsible

³ Paris méd., 1921, 11, 407 (quoted by Webster, Note 2).

⁴ Lymphocytosis as a Diagnostic Sign of Chronic Periapical Dental Infection in Adults, Jour. Am. Med. Assn., 1921, 77, 1308.

⁵ Leukocytosis following Internal Hemorrhage, Editorial, Jour. Am. Med. Assn., 1923, 81, 479.

seem to be associated with initial clotting and with the entrance of the blood into a serous cavity as shown by the work of Wright and Livingston,⁶ who demonstrated that intraperitoneal and subdural hemorrhage are always associated with a leukocytosis reaching its maximum about ten hours after the occurrence of the hemorrhage and showing a slow drop to normal over a period of several days following. Levinson⁷ has also emphasized the necessity of remembering in abdominal conditions that a leukocytosis is not necessarily indicative of sepsis, as it also occurs with abdominal hemorrhage.

Evans⁸ has recently noted a possible prognostic value for the differential count in pernicious anemia. He shows that the increase in the antihemolytic power of the blood whereby remissions occur in this disease is frequently associated with an increase in the percentage of polymorphonuclear cells and that this finding may be utilized to foretell the approach of a remission or *vice versa*. He ascribes the polymorphonuclear leukocytosis to a probable improvement in the bone-marrow function.

Simon⁹ emphatically endorses what he speaks of as the "septic factor." An absence or decrease in the number of eosinophiles associated with an increase in the percentage of polymorphonuclear neutrophils and which he finds to be almost invariably present in pyogenic infections.

He believes that, in a supposed infection of this character, if, in the presence of an increased number of polymorphonuclear neutrophils there is a normal or increased number of eosinophiles, the inference is warrantable that either the diagnosis is wrong or that the condition is being successfully overcome.

He also gives a useful table indicating the more common conditions in which the white cell count is increased, which is reproduced in Table I.

Jones and Brown¹⁰ hold the opinion that an increase in the percentage of lymphocytes, if not excessive, is a favorable sign, while a decrease below the normal is of unfavorable import.

Graphic Methods of Representing the Significance of Leukocyte Counts. Of these there are several which are often of signal value in following the course of a particular case and which present the evidence more vividly than can be grasped from a succession of laboratory reports, each bearing the statistical results as usually reported. To obtain the greatest value from leukocyte counts,

⁶ The Leukocytosis of Internal Hemorrhage, New York State Med. Jour., 1923, 23, 286.

⁷ Leukocytosis, a Deceptive Sign in Abdominal Hemorrhage, Jour. Am. Med. Assn., 1915, 64, 1294.

⁸ Subjective Symptoms and the Differential White Blood Cell Count as aids in the Prognosis of Pernicious Anemia, Pennsylvania Med. Jour., 1923, 26, 228.

⁹ Clinical Diagnosis, tenth edition, Philadelphia, Lea & Febiger, p. 50.

¹⁰ The Clinical Significance of Total and Differential Leukocyte Counts with Special Reference to Acute Infections, AM. JOUR. MED. SCI., 1922, 164, 607.

especially as a means of recording progress, it should be emphasized again that they should be made in series.

TABLE I.—MORE COMMON CONDITIONS IN WHICH CHANGES IN THE LEUKOCYTES ARE FOUND.

A.	B.	C.
<p>NEUTROPHILIC HYPERLEUKOCYTOSIS.</p> <p>All pure infections with: Streptococci Staphylococci Pneumococci Meningococci Catarrhal micrococci Colon bacilli (Hence the common wound infections) Pneumonia Erysipelas Meningitis Appendicitis Peritonitis Tonsillitis Salpingitis Puerpera sepsis Diphtheria Acute rheumatism Empyema Various abscesses Cancer, with ulceration Hemorrhage Poisons Toxemia (bacterial or of food origin) Anaphylaxis</p>	<p>NEUTROPHILIC LEUKOPENIA.</p> <p>Typhoid fever Paratyphoid fever Measles Chronic, subacute tuber- culosis Influenza Pernicious anemia Splenic anemia</p>	<p>LYMPHOCYTOSIS.</p> <p>Acute and chronic lym- phatic leukemia Pertussis Rickets Congenital syphilis Measles Typhoid fever Tuberculosis Influenza Paresis Diseases involving duct- less glands</p>
D.	E.	F.
<p>LYMPHOPENIA.</p> <p>The various diseases asso- ciated with an increase in the polymorphonu- clear neutrophiles</p>	<p>HYPEREOSINOPHILIA.</p> <p>Myelocytic leukemia Bronchial asthma Scarlatina Various skin diseases Helminthic infestations Gonorrhea Active tuberculosis During convalescence from pyogenic diseases men- tioned in Column A</p>	<p>HYPOEOSINOPHILIA.</p> <p>Noted in all the condi- tions mentioned in Col- umn A</p>
G.	H.	I.
<p>SPLENOCYTOSIS.</p> <p>Rickets Syphilis von Jaksch's anemia Typhoid fever Smallpox Mycosis fungoides Chronic malaria Kala-azar</p>	<p>HYPERBASOPHILIA.</p> <p>Asiatic cholera Myelocytic leukemia</p>	<p>MYELOCYTOSIS.</p> <p>Myelocytic leukemia The various pyogenic in- fections noted in Col- umn A Pernicious anemia Severe secondary anemia</p>

A simple chart is readily improvised from the usual squared paper used for temperature or similar records by marking the cross-lines with figures representing the white cell count in thousands, beginning at 6500 and running to 30,000 in multiples of 1000. A graphic record of the rise and fall of the total white cell count is thus readily obtained which shows many things at a glance. This method, of course, is crude and simple, but is better than none. Many more valuable are obtainable but do not seem to have come into use as widely as they should.

Another simple form of chart is the so-called "Gibson chart" which is represented in Chart I, the purpose of which is to show at a glance the ratio between the total white cell count and the polymorphonuclear percentage.

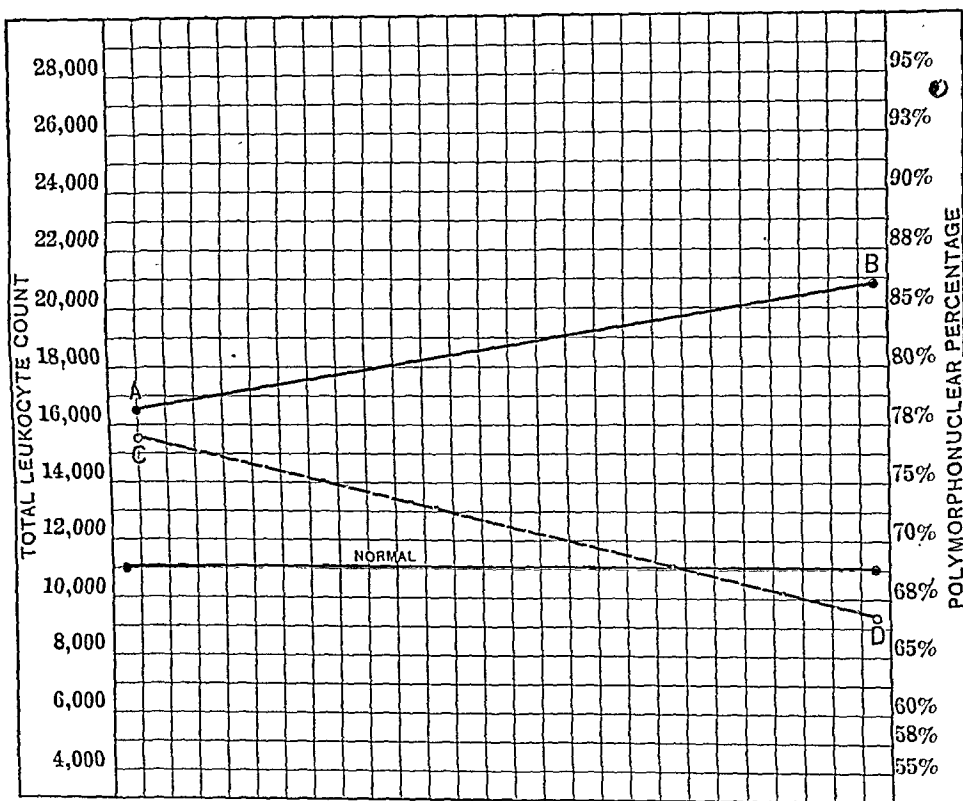


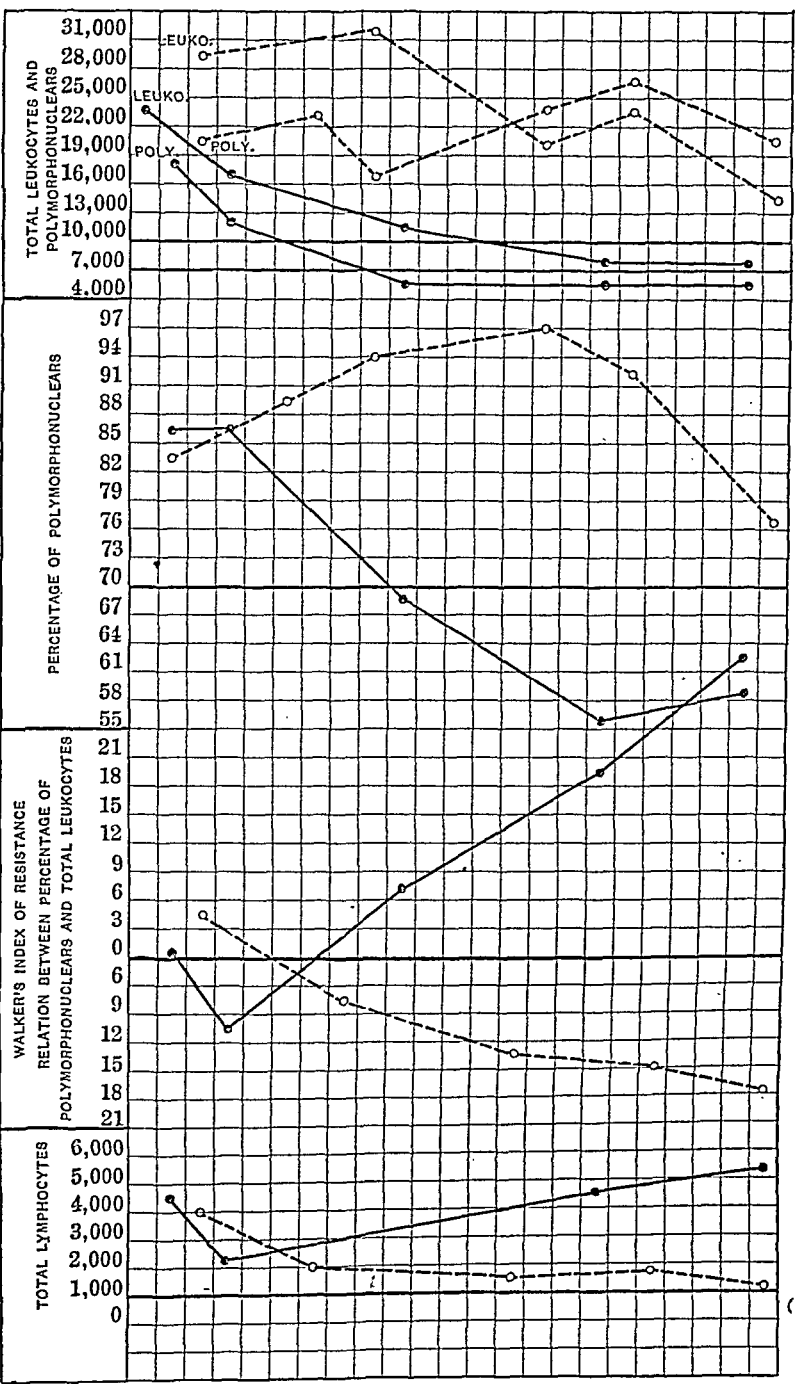
CHART I.—The Gibson chart.

The figures to the left of the chart indicate the total white cell count; those at the right hand margin the polymorphonuclear percentage. A line drawn from one to the other gives visual evidence of the degree to which the resisting powers of the patient are being utilized. In the chart the line A-B indicates a good resistance; the line C-D justifies an unfavorable inference.

Walker¹¹ has elaborated this conception somewhat and has com-

¹¹ An Index of Body Resistance in Acute Inflammatory Processes, Jour. Am. Med. Assn., 1919, 82, 1453.

puted a very useful "index of body resistance." Taking 10,000 as the highest possible normal total white cell count, and 70 as the highest possible normal polymorphonuclear percentage, he assumes



Typical favorable findings: ●——●
Typical unfavorable findings: ○——○
CHART II.—Graphic blood count chart. (After Jones and Brown.)

that for every 1 per cent increase in the polymorphonuclear count there should be a corresponding rise in the total white cell count of 1000. For example, if the polymorphonuclear count is found to be 80 (10 above 70) the total white cell count should be 20,000 (10,000 above 10,000). The index in this case would be normal or zero, that is, no variation from the normal ratio. If, however, assuming a polymorphonuclear count of 80, the total white cell count were 25,000—or 5000 over and above the assumed ratio, then the index would be plus 5, and so on; if under the same circumstances the white cell count were only 15,000 with a polymorphonuclear count of 80, then the index lacking 5000 of the proportionate number expected, would be minus 5.

A positive or plus index is of favorable import; a negative index is, as a rule, unfavorable.

Jones and Brown have endeavored to combine all of this information in a single and very useful chart shown in Chart II. To make the chart the following data are required:

1. The total white cell count.
2. The polymorphonuclear percentage—obtained from the differential count.
3. The total number of polymorphonuclear cells: ascertained by multiplying the total count by the percentage of polymorphonuclears.
4. The total lymphocyte count per c.mm.: Obtained in the same manner.
5. Walker's index: Obtained as already described.

They describe the chart as follows: "The line in the upper portion of the figure opposite 10,000 represents the highest possible normal number of total leukocytes. The first line below this designates 7000 as the highest total number of polymorphonuclear cells. The line on a level with 70 designates the highest normal polymorphonuclear percentage. The line to the right from zero denotes normal resistance according to Walker's index. The lowest line on the right side indicates 1000 as the lowest possible normal number of lymphocytes per c.mm."

The vertical columns of arabic numerals are so arranged that exactly the same amount of space is allowed for a change of 1000 in the total leukocytes or total polymorphonuclears, for a variation of 1 per cent in the polymorphonuclears, and for a shifting of one point in Walker's index. The vertical columns under "total lymphocytes" have no definite relations as above described.

It seems that there should be a wide field of usefulness for such a graphic representation of blood counts as practically forcing the more accurate correlation and interpretation of the results obtained. Of course, as always, the interpretation is what gives a blood count any value and in this connection the following conclusions seem warranted:

1. Graphic representations of blood count findings are of more value than mere rows of figures and should be more widely resorted to.

2. The curve of a series of blood counts has more diagnostic and prognostic value than a single or isolated examination. A single enumeration, however, is not without some value when interpreted in the light of all the other data obtainable.

3. The total number of white cells is, in general, in proportion to the total polymorphonuclear count. Jones and Brown, however, emphasize that a divergence of these lines is most marked as the patient returns to normal while their convergence is a bad prognostic sign.

4. While a high polymorphonuclear percentage is indicative of severe infection, in the interpretation of a low polymorphonuclear percentage the general resisting powers of the patient must be taken into consideration; it may be an indication of the overwhelming force of the infection.

5. Walker's index, when normal, must be interpreted in the light of the features of other examinations made upon the patient; if the polymorphonuclear percentage is high, the normal index is of unfavorable import (Jones and Brown). The same workers report the observation that the total lymphocyte count parallels Walker's index.

Inferences based entirely upon numerical findings of the leukocyte count are not always to be relied upon and are best considered in the light of all the other clinical findings.

There has been a recent application of the leukocyte count to the diagnosis of hepatic conditions known as the *crise hemoclasique* of Widal. While the method is of recent development, it promises to be of some value in the detection of hepatic lesions.

It is based upon the fact that the normal response to the ingestion of proteins is a leukocytosis which is held to be associated with the arrest or transformation by the liver of the peptones, proteosis, and other disintegrating substances of protein origin found in the portal vein during the digestive period. When by reason of various pathological changes the liver is deficient in this "proteopexic" function, the ingestion of proteins is followed by a leukopenia instead of a leukocytosis which constitutes the *crise hemoclasique*.

The technic of the test is simple: After a five-hour fast—which is an essential preliminary—the total number of leukocytes is counted as usual and the patient given a glass (200 gm.) of milk. Leukocyte counts are then made every twenty minutes for two hours and the results charted. Normally, because of the ingestion of the protein, a slight leukocytosis occurs, usually within the first hour of the count, at all events does not drop below the original level. A leukopenia is taken as evidence of hepatic insufficiency. Other particulars of the reaction are a low blood-pressure, and an increased coagulation-time together with a decreased sero-refractive index; the leukopenia, however, is the most delicate sign and the easiest detected.

It is obvious, of course, that spontaneous variations in the leukocyte count are a possible source of error. Glaser and Buschman,¹² indeed, believe that this factor robs the test of much of its value, having found, in an examination of 333 patients, a spontaneous change in the count averaging 2000 per c.mm. in 55 per cent and even in 90 per cent if the counts were repeated on three days.

Feinblatt,¹³ however, in a study of 80 normal subjects found that the normal response to the test was uniformly a leukocytosis and believes the test to be of value.

The exact nature of the reaction remains to be elucidated. Moutier and Rachet¹⁴ found that the reaction—negative or positive—could be produced with the ingestion of distilled water as well as of milk and believe the crisis to be due to neurovascular reflexes which are independent of the chemical nature of the test substance.

Delbecq¹⁵ believes that excitation of the pneumogastric nerve plays a part in the production of the hemoclastic crisis and that the rapidity with which the milk is ingested and the consequent degree of mechanical irritation, the temperature of the fluid, and the secretion of pepsin are all contributing factors.

The test is apparently giving consistent results though its exact status remains to be determined by future studies.

Summary. While the counting of blood cells and especially white blood cells is a most frequently utilized laboratory procedure, the correlation of the results with the clinical data is not attained to the fullest extent by reports which give simply the tabulated numerical findings. To call attention to this fact and to urge the greater usefulness of graphic methods of reporting these findings is the purpose of the present communication.

COMPOSITION AND PHYSICAL PROPERTIES OF NORMAL HUMAN BLOOD: A COMPILATION OF VALUES FROM THE LITERATURE.

By H. C. GRAM, M.D.,

(ROBERT M. GIRVIN FELLOW IN RESEARCH MEDICINE AND FELLOW OF THE ROCKEFELLER FOUNDATION.)

(From the John Herr Musser Department of Research Medicine, University of Pennsylvania, Philadelphia.)

THE chemical, physical and morphological examination of the blood every day gains more and more importance in practical and

¹² Spontaneous Variations in the Leukocyte Count, *Med. Klin.*, 1923, 19, 1143.

¹³ Leukocytosis in Eighty Normal Men: A Study in Reference to the Crise Hémoclasique of Widal, *Jour. Am. Med. Assn.*, 1923, 80, 613.

¹⁴ Hemoclastic Crises, *Prog. méd.*, 469.

¹⁵ Leukopenia in Shock, *Paris méd.*, 1922, 13, 218.

scientific medicine. It is impossible to peruse a medical periodical without coming upon statements of pathological values for one or more blood constituents. Even for the specialist in this subject it may be difficult to keep in mind the normal values required for a proper understanding of such findings. The necessary data are scattered in the fast growing literature, while the handbooks very often contain superannuated or false values. The following compilation of normal values was made for the author's own needs. It has proven so useful that it is felt worth while to make it available to others.

The values presented here have been chosen upon the following grounds. When possible, values obtained by modern methods on strictly normal subjects, not patients, have been chosen. Values which give or allow calculation of content in corpuscles and serum have been preferred to larger series on either whole blood or serum alone. Also series using both males and females have been preferred to observations on one sex only. Several sets of observations of the author have been introduced for one or other of these reasons and because of the uniformity in the manner of taking and handling of the blood.

In the following tables the maximum, minimum and average are generally given, where such are available. Sometimes, however, only the average is recorded, when the observations are too few to give any idea of the possible variations. A differentiation between men and women is generally made only where an acknowledged sex difference is present or in some cases because the tables quoted were so arranged.

I. THE ORDINARY AND MORPHOLOGICAL BLOOD EXAMINATION. Hemoglobin, erythrocytes, differential leukocytes, count, the Arneth blood picture, reticulated erythrocytes, cell volume, diameter of erythrocytes, color index, volume index, ratio hemoglobin
cell vol. per cent

TABLE I.—HEMOGLOBIN PER CENT.

100 per cent = 18.5 volume per cent oxygen capacity = 13.8 gm. hemoglobin per 100 cc.)

	Bie and Moeller. ¹ (Meisling colorimeter standardized by gas pump oxygen determina- tions.)				Gram and Norgaard. ² (Autenrieth colorimeter standardized by Van Slyke oxygen determina- tions.)			
	Men.		Women.		Men.		Women.	
	Per cent.	Gm. per 100 cc.	Per cent.	Gm. per 100 cc.	Per cent.	Gm. per 100 cc.	Per cent.	Gm. per 100 cc.
Maximum . . .	120	16.6	101	13.9	118	16.3	102	14.1
Minimum . . .	99	13.7	89	12.3	96	13.2	88	12.1
Average . . .	107	14.8	96	13.2	109	15.0	94	13.0
Subjects . . .	10	...	10	...	10	...	10	...

TABLE II.—ERYTHROCYTES: MILLIONS PER 1 C.MM. BLOOD.

	Bie and Moeller. ¹		Gram and Norgaard. ²		Gram. ³	
	Men.	Women.	Men.	Women.	Men.	Women.
Maximum	6.395	5.21	5.91	5.05	5.82	5.33
Minimum	4.99	4.25	4.85	4.36	4.85	4.21
Average	5.53	4.74	5.45	4.65	5.37	4.78
Subjects	10	10	10	10	32	56

TABLE III.—LEUKOCYTES PER 1 C.MM.

	Men.	Women.
Maximum	9200	10300
Minimum	4400	4600
Average	6300	7200
Subjects	25	24

The values are very labile. Data in table refer to venous blood of fasting normal individuals.⁴

TABLE IV.—DIFFERENTIAL COUNT IN PER CENT OF TOTAL LEUKOCYTES.

	Naegeli. ⁵	Pappenheim. ⁶
Lymphocytes	22-25	23
Monocytes	3-5	2-6
Neutrophiles	65-70	65-72
Eosinophiles	2-4	2-4
Basophiles	0.5	0.5

The number of subjects are not given.

TABLE V.—THE ARNETH BLOOD PICTURE.

(Number of nuclear segments in neutrophile leukocytes.)

1 segment	2 segments	3 segments	4 segments	5 or more segments
5 per cent	35 per cent	41 per cent	17 per cent	2 per cent

Number of subjects are not quoted.^{7 8}

TABLE VI.—PERCENTAGE OF RETICULATED ERYTHROCYTES.

Less than 1 per cent.^{9 10}

TABLE VII.—CELL VOLUME PERCENTAGE.*

	Gram and Norgaard ² (Hirudin-blood, hematokrit).		Gram ^{11 12} (Citratd blood, larger tubes).	
	Men.	Women.	Men.	Women.†
Maximum	50.0	43.0	51	45
Minimum	42.4	38.8	43	36
Average	46.3	40.6	48	40
Subjects	10	10	25	96

* According to Gram and Norgaard's figures for the cell count, the average volume of a normal erythrocyte would be $85.9 \mu^3$.

† Combination of two series by same technic.

The cell volume is altered slightly by changes of reaction.

If the cell volume at pH 7.4 is called 100 it will be 104 at pH 7.8 and 96 at pH 7.0. (Warburg.¹³)

TABLE VIII.—DIAMETER OF THE ERYTHROCYTES (MEASURED IN THEIR OWN SERUM.)

Mean diameter ^{14 15}	Maximum	8.0 μ
	Minimum	7.7 μ
	Average	7.8 μ
Greatest diameter of single erythrocyte		9 μ
Smallest diameter of single erythrocyte		6 μ

TABLE IX.—COLOR INDEX.

(Calculated with 100 per cent Hemoglobin = 18.5 per cent oxygen capacity.)

Formula: Index = $\frac{\text{Hemoglobin, per cent}}{\text{Millions of cells per c.mm.} \times 20}$	
Maximum ²	1.05
Minimum	0.98
Average	1.00
Subjects	20

There is no appreciable sex variation. The normal deviation from 1.00 depends mainly on the precision of the methods employed. With ordinary clinical precision values between 0.9 and 1.1 can be considered as normal.

TABLE X.—VOLUME INDEX.

(Calculated assuming 5,000,000 normal cells per c.mm. = 42.96 volume per cent.)

Formula: V.I. = $\frac{\text{Volume per cent} \times 0.1164}{\text{Millions of erythrocytes per c.mm.}}$	
Maximum ²	1.06
Minimum	0.96
Average	1.00
Subjects	20

TABLE XI.

Ratio	Hemoglobin, per cent
	Volume per cent
Maximum ²	2.47
Minimum	2.24
Average	2.34
Subjects	20

II. FACTS PERTAINING TO COAGULATION AND HEMOSTASIS.

Platelet count, clotting-time and bleeding-time.

TABLE XII.—BLOOD PLATELETS PER 1 C.MM. BLOOD.

Maximum	540,000
Minimum	280,000
Average around	350,000
Subjects	25

These figures¹⁶ refer to venous blood by Oluf Thomsen's technic. When skin blood is used the figures tend to be lower and are much less reliable.

Coagulation-time. The coagulation-time of blood depends very much on technic and handling and whether the end-point chosen is the first appearance of fibrin or the solid clotting. A simultaneous control with normal blood should be done.

1. The more contact, the quicker the coagulation.

2. The higher temperature, the quicker the coagulation.

3. Blood from skin cuts clots quicker than venous blood.

The following values are for venous blood in test-tubes.

TABLE XIII.—COAGULATION-TIME.

Normal values min.	Stage of coagulation taken as end-point.	Characteristics of method.	Temperature, °C.	Author.
Average 6½	Middle	Immobility of surface of 1 cc blood in test-tube	37	Lee and White. ¹⁷
3 to 8 . . .	Middle	Immobility of surface of 1 cc blood in test-tube	35	Gram. ¹⁸
Average 2 . .	Beginning	Adhesion of fibrin to wire loop moved in 20 cc blood kept in test-tube	37	Bachrach and Tittinger. ¹⁹

TABLE XIV.—BLEEDING-TIME. (DUKE.)

Maximum ¹⁶	4 minutes
Minimum	1½ "
Subjects	100

III. ARTERIAL AND VENOUS BLOOD.

TABLE XV.—SYNOPSIS OF DIFFERENCE BETWEEN ARTERIAL AND VENOUS BLOOD.²⁰

	Arterial.	Venous.
pH* (plasma) . . .	7.30 to 7.40	7.27 to 7.37
Free CO ₂ (blood)† . .	1.5 to 4.0 vol. per cent (0.67 to 1.8 m-M per L.)	1.7 to 4.2 vol. per cent. (0.76 to 1.87 m-M per L.)
Bound CO ₂ † . . .	31 to 56 vol. per cent (14 to 25 m-M per L.)	36 to 61 vol. per cent. (16 to 27 m-M per L.)
or BHCO ₃ (blood) . . .		
Plasma-Cl† (as NaCl) .	0.614 to 0.642 gm. per 100 cc (105 to 110 m-M per L.)	0.596 to 0.625 gm. per 100 cc. (102 to 107 m-M per L.)
Percentile oxygen** saturation of hemoglobin .	93 to 98 per cent	62 to 85 per cent.
Oxygen** content . .	17 to 22 vol. per cent (7.6 to 9.8 m-M per L.)	11 to 16 vol. per cent. (4.9 to 7.0 m-M per L.)

* See also Table XXX.

† See also Table XIX.

‡ See also Table XXVI.

** See also Table XVII.

IV. GASES OF THE BLOOD. Oxygen capacity, oxygen content and unsaturation, total CO₂, free and bound CO₂.

TABLE XVI.—OXYGEN CAPACITY (= VOLUME PER CENT OXYGEN REDUCED TO 0° C. AND 760 MM. HG. BOUND BY 100 CC OF BLOOD).

(Calculated by Gram and Norgaard and Bie and Moeller's colorimetric data. Formula: 18.5 volume per cent O₂ = 100 per cent hemoglobin. See Table I of hemoglobin.)

	Bie and Moeller. ¹		Gram and Norgaard. ²	
	Men.	Women.	Men.	Women.
Maximum	22.2	18.7	21.8	18.9
Minimum	18.3	16.5	17.8	16.1
Average	19.8	17.8	20.2	17.4
Subjects	10	10	10	10

TABLE XVII.—OXYGEN CONTENT AND OXYGEN UNSATURATION OF VENOUS BLOOD OF MALES* (VAN SLYKE TECHNIC).

	Oxygen content, vol. per cent.	Oxygen unsaturation, vol. per cent.†
Maximum ²¹	17.98	8.95
Minimum	9.55	2.70
Average	13.60	5.80
Subjects	12	12

* See also Table XV of differences between arterial and venous blood.

† Oxygen unsaturation = oxygen capacity — oxygen content.

Dissolved oxygen and nitrogen (reduced):

	Vol. per cent.
Blood saturated with air at room temperature	2.11
Arterial blood	1.70
Venous blood	1.50

TABLE XVIII.—TOTAL CO₂ OF VENOUS OXALATED PLASMA AND BLOOD OF MALES* (VAN SLYKE TECHNIC).

	Plasma.		Blood.	
	Volume per cent.	Millimol per L.	Volume per cent.	Millimol per L.
Maximum ²²	70.8	31.6	61.2	27.3
Minimum	59.6	26.6	52.0	23.2
Average	67.7	30.2	57.4	25.6
Subjects	14		23	

$$\text{Millimols CO}_2 \text{ per L.} = \frac{\text{Volume per cent CO}_2}{2.24\ddagger}$$

* See also Table XV of differences between arterial and venous blood.

† According to Warburg 2.2263 for CO₂. Biochem. Jour., 1922, 16, 11.

TABLE XIX.—FREE AND BOUND CO₂ OF VENOUS PLASMA.

(Calculated from data of Cullen and Robinson by Hasselbalch's equation:

$$[\text{pH} = \text{pK}_1 + \log \frac{\text{BHCO}_3}{\text{H}_2\text{CO}_3}] \text{ with } \text{pK}_1 = 6.1)$$

	Plasma, m-M per L.	
	H ₂ CO ₃ .	BHCO ₃ .
Maximum	1.9	30.2
Minimum	1.3	26.4
Average	1.6	28.6
Subjects	14	

V. VARIOUS SUBSTANCES IN SERUM (PLASMA), CORPUSCLES AND WHOLE BLOOD. Inorganic constituents of serum, inorganic constituents of corpuscles, inorganic constituents of blood, acid-base composition of venous plasma, phosphoric acid compounds and inorganic phosphorus, lactic acid, chloride, non-protein nitrogen, total nitrogen, hydrogen-ion concentration, bile pigment and plasma color, sugar, dry substance, serum proteins, ratio $\frac{\text{albumin}}{\text{globulin}}$, fibrin.

TABLE XX.—CONTENT OF INORGANIC SUBSTANCES IN SERUM (PLASMA).*

	Milligrams per 100 cc.	Millimols per L.	Sub- jects.	Author.
Cl†	357-381	100.60-107.60	10	Gram, H. C. ²¹
S	0.5-0.9	0.16- 0.28	10	Denis, W., and Hobson, S. ²⁴
P† (inorg.)	3.2-4.3	1.03- 1.39	22	Tisdall, F. ²⁵
K	18-21	4.60- 5.40	26	Kramer, B., and Tisdall, F. ²⁶
Na	326-350	141.70-152.20	18	Kramer, B., and Tisdall, F.
Ca	9-11	2.25- 2.75	8	Halverson, Mohler and Bergein. ²⁸
Mg	2.2-3.5	0.91- 1.40	?	Marriott, W. McK. and Howland, J. ²⁹
NH ₄ (calculated as NH ₃)	0.14-0.3	0.01- 0.02	6	Morgulis, S., and Jahr, H. M. ³⁰

* Values recalculated into milligrams per 100 cc and millimols per L. Chlorides, phosphates and sulphates stated as Cl, P and S.

† See, however, Table XXVI of chlorides concerning the influence of the CO₂ content.

‡ Compare the lower values to be calculated from Bloor's result in Table XXIIIa of phosphoric acid compounds.

TABLE XXI.—AVERAGE CONTENT OF INORGANIC SUBSTANCES IN THE CORPUSCLES.*

	Milligrams per 100 cc.	Millimols per L.	Sub- jects.	Author.
Cl†	186	52.50	22 (27 obs.)	Gram, H. C., and Norgaard, A. ³¹
S (inorg.): Nearly same content as that of serum.			See Tables XX and XXII.	
P (inorg.)	5.44	1.75	27	Bloor, W. R. ³²
K	425	109.00	..	See footnote ‡.
Na	43	18.80	1	Schmidt, C.; quoted by Matthews, A. P. ³³
Ca	3.47	0.87	1	Cowie, D. M., and Calhoun, H. A. ³⁴
Mg. Nearly same content as that of serum.			See Tables XX and XXII.	

* Some of these values are uncertain, being based on few determinations or somewhat doubtful calculations.

† See, however, Table XXVI of chlorides concerning the influence of the CO₂ content.

‡ K content calculated by using the average figures in two series by Kramer and Tisdall: K serum, 19.7 mg. per 100 cc; K blood, 182 mg. per 100 cc, with an average cell volume of 40 per cent. The corresponding calculation for sodium, however, gives a negative value, wherefore Schmidt's single determination has been used.

TABLE XXII.—CONTENT OF INORGANIC SUBSTANCES IN WHOLE BLOOD.

	Milligrams per cc.	Millimols per L.	Sub- jects.	Author.
Cl	273-321	77.00-90.60	15	Gram, H. C., and Norgaard, A. ³¹
S (inorg.)	0.5-1.1	0.16- 0.34	10	Denis, W. ³⁵
P (inorg.):	Between values for serum and corpuscles.		See	Tables XX and XXI.
K	153-201	39.20-51.60	13	Kramer, B., and Tisdall, F. ³⁶
Na	170-225	73.90-97.80	6	Kramer, B., and Tisdall, F. ³⁷
Ca	5.3-6.8	1.30- 1.70	13	Kramer, B., and Tisdall, F. ³⁸
Mg	2.3-4.0	0.90- 1.60	8	Kramer, B., and Tisdall, F. ³⁹

Values more variable than those for serum and corpuscles on account of the uneven distribution and different cell volumes.

TABLE XXIIIa.—PHOSPHORIC ACID COMPOUNDS IN PLASMA AND CORPUSCLES (BLOOD).

Milligrams H_3PO_4 per 100 cc.⁴¹

(To transform into P use equation: $P = 0.316 H_3PO_4$.)

Men.	Plasma.					Corpuscles.				
	Total.	Acid soluble.	Inorg.	Lipoid.	Other forms.	Total.	Acid soluble.	Inorg.	Lipoid.	Other forms.
Men:										
Maximum	43.5	13.7	12.0	23.3	4.00	325.0	250.0	27.3	66.6	238.0
Minimum	24.3	7.5	6.0	16.0	0.40	185.0	140.0	12.0	43.5	123.0
Average	32.0	10.4	8.7	22.1	1.70	248.0	188.0	18.7	57.0	172.0
Subjects	17					17				
Women:										
Maximum	41.0	14.3	13.8	29.0	4.00	265.0	206.0	26.3	62.5	188.3
Minimum	31.0	9.4	8.0	19.0	0.00	218.0	160.0	9.8	47.0	133.7
Average	36.2	12.4	11.2	24.9	1.26	249.0	187.0	15.7	56.6	167.0
Subjects	10					10				

Definitions of fractions:

1. Acid-soluble: Soluble in dilute acids and precipitated with the proteins by alcohol-ether.

2. Lipoid: Soluble in alcohol-ether and precipitated with the proteins by dilute acids.

3. In the first group are included inorganic phosphorus and an unknown compound; in the second substances of the type of lecithin.

TABLE XXIIIb.—INORGANIC PHOSPHORUS IN SERUM* (TISDALL'S TECHNIC).

	Milligrams of P per 100 cc. ⁴²
Maximum	4.3
Minimum	3.2
Average	3.8
Subjects	22

* Higher values 6.4 to 4.6, average 5.4 mg. per 100 cc in serum of children.

TABLE XXIV.—AVERAGE ACID-BASE COMPOSITION OF VENOUS PLASMA.⁴⁰

	Cations, milliequivalents per L.		Anions, milliequivalents per L.
Na	143.4	HCO ₃	27.0
K	5.1	Cl	103.0
Ca	5.0	HPO ₄	3.0
Mg	2.5	SO ₄	1.0
		Organic acids	2.0
		Proteins*	20.0
Sum	156.0	Sum	156.0

* Calculated by differences.

The ammonium value is too small to be considered. The values in grams or millimols can be calculated from atomic weight and valency.

Atomic weights: H 1, Na 23, K 39, Ca 40, Mg. 24, C 12, O 16, N 14, P 31, S 32, Cl 35.5.

Physiological valency: Ca 2, Mg. 2, SO₄ 2, HPO₄ 1.8.

1 gm. molecule = 1000 millimols.

Millimols \times valency = milliequivalents = cc of 0.1 normal per 100 cc.

TABLE XXV.—LACTIC ACID IN WHOLE BLOOD OF CHILDREN (CLAUSEN TECHNIC).

	Milligrams per 100 cc. ⁴³	Millimols per L.
Maximum	35	3.9
Minimum	18	2.0
Average	25	2.8

Number of subjects not given.

TABLE XXVI.—CHLORIDE as NaCl IN SERUM OR PLASMA.

(From whole blood exposed to air with loss of CO₂.)

	Gram ²³ (modified Austin and Van Slyke technic).		Gram and Norgaard ⁴⁴ (modi- fied Bang technic).	
	Milligrams per 100 cc serum.	Millimols per L. serum.	Milligrams per 100 cc hirudin plasma.	Millimols per L. hirudin plasma.
Maximum	629	107.6	625	106.9
Minimum	588	100.6	595	101.8
Average	604	103.3	613	104.9
Subjects	10	...	7	

(12 determinations)

The chloride content of the whole blood depends largely on the cell volume, as the cells contain only approximately half as much Cl as the serum. The distribution between serum and cell changes with the variation in the CO₂ content of the blood, so that the concentration of Cl of serum decreases with increasing CO₂ content (see Table XV of differences between arterial and venous blood). In 15 presumably normal persons Gram and Norgaard³¹ found on the average, 0.31 per cent, calculated as NaCl, in the corpuscles; a later series of 12 determinations on 7 strictly normal persons gave an average of 0.304 per cent NaCl. On whole blood (cell volume 40 to 50 per cent) the same authors found 0.45 to 0.53 per cent NaCl, while Gettler and Baker⁴⁵ found from 0.4 to 0.531 per cent.

TABLE XXVII.—LIPOIDS IN WHOLE BLOOD, PLASMA AND CORPUSCLES (BLOOR TECHNIC).

Averages in grams per 100 cc. ⁴⁶			
	Men.	Women.	
Total fatty acids:			
Blood	0.36	0.36	
Plasma	0.38	0.40	
Corpuscles	0.35	0.29	
Lecithin:			
Blood	0.30	0.29	
Plasma	0.22	0.19	
Corpuscles	0.40	0.44	
Cholesterin:			
Blood	0.21	0.23	
Plasma	0.22	0.24	
Corpuscles	0.19	0.21	
Fat:			
Plasma	0.14	0.16	
Corpuscles	0.07	0.00	
Total lipoids:			
Plasma	0.67	0.69	

Number of subjects not given.

TABLE XXVIIIa.—NON-PROTEIN NITROGEN AND ITS FRACTIONS IN BLOOD, PLASMA AND CORPUSCLES.

Milligrams N. per 100 cc. of blood. ⁴⁷			
	Maximum.	Minimum.	Average.
Blood:			
Amino-acid N.	7.8	5.7	6.4
Urea N.*	15.2	8.9	11.5
Undetermined N	17.5	10.1	13.7
Total non-protein N.	39.4	27.8	32.1
Plasma:			
Amino-acid N.	6.2	4.3	5.3
Urea N.*	17.3	9.6	12.4
Undetermined N	11.5	1.8	6.7
Total non-protein N.	30.0	18.0	24.7
Corpuscles:			
Amino-acid N.	10.7	6.7	8.2
Urea N.*	13.2	7.7	10.3
Undetermined N.	33.8	18.3	24.7
Total non-protein N.	55.0	37.7	43.6

Subjects, 12

* To transform into milligrams urea use equation: Urea = 2.125 urea N.

TABLE XVIII^b.—QUANTITIES OF SOME OTHER NITROGEN-CONTAINING CONSTITUENTS IN THE WHOLE BLOOD.⁴⁸

	Milligrams per 100 cc. of blood.
Uric acid	0.7-3.0
Creatinin	1.2-1.5
Creatin (mainly in corpuscles)	3.5-5.0
Number of subjects not given.	

TABLE XXIX.—TOTAL NITROGEN OF SERUM AND BLOOD.

	Serum.*	Blood,† gm. per 100 cc.
Maximum ⁴⁵	1.43	4.10
Minimum	1.20	3.00
Average	1.31	3.43
Subjects	30	30
		Fibrin per cent

* Plasma should show slightly higher figures by as much as $\frac{6.25}{6.25}$ See

Table XXXVI of fibrin content of plasma.

† The total N. of blood depends partly on cell volume as the corpuscles contain more protein and also more non-protein nitrogen than the serum.

TABLE XXX.—HYDROGEN-ION CONCENTRATION (EXPRESSED AS pH) IN VENOUS OXALATED PLASMA OF MEN.*

	pH.
Maximum ²²	7.41
Minimum	7.28
Average	7.36
Subjects	27

* Precautions against loss of CO₂. Colorimetric determination of Cullen corrected to pH electrometric at 38° C.

The corpuscles are somewhat more acid (that is, pH is 0.10 to 0.15 smaller). Arterial plasma is about 0.03 pH more alkaline. See Table XV of differences between arterial and venous blood.

TABLE XXXIa.—PLASMA COLOR.

(Meulengracht⁹ plasma color: Volume of 1 cc plasma diluted to equality of color with a chromic standard color.)

Men	1 to 5
Women	1 to 3
Subjects: 34 men and 40 women.	

TABLE XXXI^b.—BILE PIGMENT OF SERUM.

(Bilirubin units of van den Bergh⁴⁹ = 1 unit = 0.5 mg. in 100 cc.)
Normal = 0.5 to 1 unit.

TABLE XXXII.—SUGAR (DEXTROSE) IN BLOOD, PLASMA AND CORPUSCLES. (FASTING INDIVIDUAL. HAGEDORN TECHNIC.)

	Milligrams per 100 cc.*		
	Blood.	Plasma.	Corpuscles.
Maximum ⁵⁰	116	114	121
Minimum	79	77	77
Average	99	98	100
Subjects	28	28	28

* To transform into m-M per L. use equation: m-M per L. = 0.0556 × mg. per 100 cc.

After the meals the values are much more variable.

TABLE XXXIII.—DRY SUBSTANCE OF SERUM, BLOOD AND CORPUSCLES.¹

	Serum, gm. per 100 gm.		Blood, gm. per 100 gm.		Corpuscles, gm. per 100 gm.	
	Men.	Women.	Men.	Women.	Men.	Women.
Maximum	9.750	9.395	21.820	19.755	35.730	36.630
Minimum	8.555	8.400	19.915	18.010	33.100	33.470
Average	9.010	8.770	20.890	18.990	34.606	35.193
Subjects	10	10	10	10	10	10

To convert into grams per 100 cc multiply by average specific gravities in Table XLI.

TABLE XXXIV.—TOTAL SERUM PROTEINS.

	Gram ²³ (refractometric), gm. per 100 cc.	Gettler ⁴⁵ (from nitrogen),* gm. per 100 cc.	Atchley. ⁵¹	
			(refractometric), gm. per 100 cc.	(from nitrogen), gm. per 100 cc.
Maximum	8.8	8.7	8.5	8.1
Minimum	7.7	7.3	7.4	7.2
Average	8.05	8.0	8.0	7.5
Subjects	10	30	18†	18†

* Calculated from these authors total nitrogen figures, subtracting the average non-protein nitrogen of serum and multiplying by 6.25. See Tables XXVIIIa and XXIX of non-protein nitrogen and total nitrogen.

† 28 determinations.

‡ 26 determinations.

TABLE XXXV.—RATIO $\frac{\text{ALBUMIN}}{\text{GLOBULIN}}$ OF SERUM.

	Alder ⁵² (Rohrer's technic).	Linder ⁵³ (Howe's technic).
Maximum	4.0	2.0
Minimum	1.2	1.2
Average	1.6
Subjects	62	12

TABLE XXXVI.—FIBRIN IN PLASMA AND BLOOD (GRAM'S TECHNIC).¹¹

	Plasma, gm. per 100 cc.		Blood, gm. per 100 cc.	
	Men.	Women.	Men.	Women.
Maximum	0.36	0.38	0.19	0.21
Minimum	0.20	0.21	0.11	0.12
Average	0.27	0.29	0.14	0.17
Subjects	25	25	25	25

The percentage per 100 cc blood depends to a large extent on the cell volume.

VI. SOME PHYSICAL PROPERTIES OF BLOOD AND ITS CONSTITUENTS. Resistance of corpuscles to hypotonic salt solutions, sedimentation of corpuscles, freezing-point depression of serum, conductivity and corrected conductivity of serum, specific gravity of serum and corpuscles, viscosity of serum and blood, refractive index of serum.

TABLE XXXVII.—RESISTANCE AGAINST HYPOTONIC SALT SOLUTIONS.

(1 drop corpuscles in 2 cc solution.¹⁵)

	NaCl, per cent.
Beginning hemolysis	0.48-0.42
Half hemolysis	0.42-0.38
Total hemolysis	0.38-0.32
Subjects	20

TABLE XXXVIII.—SEDIMENTATION OF THE CORPUSCLES.

(Measured by the height of the plasma layer.)

	Gram ⁵⁴ (Blood column 50 mm. high, 1 part 3 per cent Na citrate and 9 parts blood.) After one hour.		Fähræus ⁵⁵ (Blood column 150 mm. high, 1 part 2 per cent Na citrate and 4 parts blood.) After one hour.	
	Men. mm.	Women. mm.	Men. mm.	Women mm.
Maximum	5	13	9.0	29.0
Minimum	Less than 1	2	0.5	2.0
Average	Less than 2	6	3.3	7.4
Subjects	10	10	82	61

TABLE XXXIX.—FREEZING-POINT DEPRESSION (Δ) OF SERUM AND ITS EQUIVALENTS IN NaCl AND NON-DISSOCIATED CRYSTALLOIDS.

	Δ —° C.	NaCl equivalent. ⁵⁶		Equivalent of non-dissociated crystalloids,* Millimols per L.
		Grams per 100 cc.	Millimol per L.	
Maximum ²³	0.570	0.972	164.6	308.1
Minimum	0.555	0.946	161.8	300.0
Average	0.562	0.958	163.9	303.8

* Depression caused by 1 gram-molecule per L. = 1.85° C.

The osmotic pressure in the cells is the same as that of the serum

TABLE XL α .—ELECTRICAL CONDUCTIVITY OF SERUM AT 20° C. AND 25° C.*

	$K_{25}^{\circ} \times 10^4$.	Gram ⁵⁷ (ionometer).		Atchley ⁵¹ (bridge), $K_{25}^{\circ} \times 10^4$.
		NaCl equivalent. Grams per per 100 cc. Millimols per L.		
Maximum	111.0	0.674	115.3	123.9
Minimum	104.8	0.640	109.5	116.5
Average	106.3	0.652	111.6	119.9
Subjects	30			18†

* Correction of NaCl equivalent for temperature between 15° and 25° is approximately +2.06 per cent for each degree rise of temperature.

† 28 determinations.

The conductivity of blood depends⁵⁷ on the cell volume. The ratio $\frac{\text{conductivity of serum}}{\text{conductivity of blood}}$ is a constant for each cell volume. These constants are 2.07 for 38 vol. per cent, 2.39 for 44 vol. per cent and 2.8 for 50 vol. per cent.⁵⁸

TABLE XLb.—SERUM CONDUCTIVITY AT 20° C. CORRECTED FOR DEPRESSING INFLUENCE OF PROTEINS.

(Formula:⁵⁹ Corr. conduct. = obs. conduct. \times 100 $100 - (2.2 \times \text{protein per cent})$

	Corrected NaCl equivalent.	
	Grams per 100 cc.	Millimols per L.
Maximum	0.811	138.8
Minimum	0.787	134.6
Average	0.799	136.7
Subjects	10	

TABLE XLI.—SPECIFIC GRAVITY OF SERUM AND CORPUSCLES AT 20° C.

	Serum (Gettler ⁶⁰).	Corpuscles (Schmidt ⁶⁰).
Maximum	1.0380	1.0889
Minimum	1.0241	1.0880
Average	1.0293	1.0885
Subjects	30	Not given.

The specific gravity of whole blood will depend mainly on cell volume and specific gravity of serum (average 1.05 to 1.06).

TABLE XLII.—VISCOSITY OF SERUM AND BLOOD.

(Hess viscosimeter at 20° C.)

	Serum.	Blood.
Maximum ⁶¹	1.7	5.4
Minimum	2.0	3.6
Number of subjects not given.		

Correction for temperature is +0.8 per cent for each degree increase of temperature between 15 and 25° C.

TABLE XLIII.—REFRACTIVE INDEX OF SERUM AT 17.5° C.

(Abbé refractometer, refractive index of distilled water being 1.33320.)

Maximum ⁶²	1.35110
Minimum	1.34920
Subjects	12

VII. TOTAL VOLUME.

TABLE XLIVa.—TOTAL BLOOD AND SERUM VOLUME (VITAL-RED METHOD).

	Plasma.		Total blood.	
	Volume, cc.	Cc per 100 gm. body weight.	Volume, cc.	Cc. per 100 gm. body weight.
Maximum ⁶³	3750	5.8	6675	10.4
Minimum	250	4.3	4200	8.2
Average	3033	5.7	5447	9.0
Subjects	24		18	
Body weight: Plasma, 74 to 51 kg.; total blood, 85 to 47 kg.				

TABLE XLIVb.—BLOOD VOLUME (CO METHOD).

	Total volume, cc.	Cc per 100 gm. body weight.
Maximum ⁶⁴	4601	6.99
Minimum	3429	5.23
Average	3888	5.95
Subjects	6 (7 determinations)	
Body weight: 72.7 to 60.9 kg.		

The discrepancy in blood volume between the results of the dye and the CO methods is mainly due to the fact that the first measures a substance in the serum from which the blood volume is calculated; the second, a substance in the cells. A combination of the two methods would give better results, eliminating the influence of a varied $\frac{\text{serum}}{\text{corpuscle}}$ ratio in the different vascular areas.⁶⁵

Summary. Forty-four tables are presented, giving the normal figures for various chemical, physical and morphological examinations of the blood.

BIBLIOGRAPHY:

1. Bie, V., and Moeller, P.: Arch. d. mal. d. cœur., 1922, 15, 177.
2. Gram, H. C., and Norgaard, A.: Arch. Int. Med., 1923, 31, 364.
3. Gram, H. C.: Ugesk. f. Læger., 1920, 82, 1543.
4. Gram, H. C.: Studier over fibrin-mængden, Copenhagen, 1921, Thesis.
5. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Leipzig, 1908.
6. Pappenheim, A.: Les leucocytes à l'état normal, Traité du sang., Paris, 1913, 1, 259.
7. Arneth: Die neutrof. weissen Blutkörperchen bei Infektionskrankheiten, Jena, 1904.
8. Arneth: Die qualitative Blutlehre, Leipzig, 1920.
9. Meulengracht, E.: Der chronische, hereditäre, hämolytische Ikterus, Leipzig, 1922.
10. Chauffard, A., and Fiessinger, N.: Bull. et mém. Soc. méd. d. hop. d. Paris, 1907, 24, 1169.
11. Gram, H. C.: Acta med., Scandinavica, 1922, 56, 107.
12. Gram, H. C.: Ugesk. f. Læger., 1920, 82, 1609.
13. Warburg, E.: Biochem. Jour., 1922, 16, 133.
14. Gram, C.: Thesis, Copenhagen, 1883.
15. Meulengracht, E.: Der chronische hereditäre, hämolytische Ikterus, Leipzig, 1922.
16. Gram, H. C.: Arch. Int. Med. (this paper gives the limits 200,000 to 550,000 on a larger number of not strictly normal persons), 1920, 25, 325.
17. Lee and White: Am. Jour. Med. Sci., 1913, 145, 495.
18. Gram, H. C.: Bull. Johns Hopkins Hosp., 1920, 31, 363.
19. Bachrach and Tittinger: Wien. klin. Wchnschr., 1910, 394.
20. Wilson, D. W.: Physiol. Rev., 1923, 3, 295.
21. Lundsgaard, C.: Jour. Biol. Chem., 1918, 33, 133.
22. Cullen, G. E., and Robinson, H.: Jour. Biol. Chem., 1923, 57, 533.
23. Gram, H. C.: Jour. Biol. Chem., 1923, 56, 593.
24. Denis, W., and Hobson, S.: Jour. Biol. Chem., 1923, 55, 183.
25. Tisdall, F.: Jour. Biol. Chem., 1922, 1, 329.
26. Kramer, B., and Tisdall, F.: Jour. Biol. Chem., 1921, 46, 348.
27. Kramer, B., and Tisdall, F.: Jour. Biol. Chem., 1921, 46, 467.
28. Halverson, Mohler and Bergein: Jour. Biol. Chem., 1917, 32, 171.
29. Marriott, W., McK., and Howland, J.: Jour. Biol. Chem., 1917, 32, 233.
30. Morgulis, S., and Jahr, H. M.: Jour. Biol. Chem., 1919, 38, 435.
31. Gram, H. C., and Norgaard, A.: Jour. Biol. Chem., 1921, 49, 264; 1923, 56, 429.

32. Bloor, W. R.: *Jour. Biol. Chem.*, 1918, 36, 49.
33. Schmidt, C., quoted by A. P. Matthews: *Physiol. Chem.*, 1915, New York.
34. Cowie, D. M., and Calhoun, H. A.: *Jour. Biol. Chem.*, 1919, 37, 505.
35. Denis, W.: *Jour. Biol. Chem.*, 1921, 49, 311.
36. Kramer, B., and Tisdall, F.: *Jour. Biol. Chem.*, 1921, 48, 223.
37. *Ibid.*
38. *Ibid.*
39. *Ibid.*
40. Gamble, Ross and Tisdall: *Jour. Biol. Chem.*, 1923, 57, 635.
41. Bloor, W. R.: *Jour. Biol. Chem.*, 1918, 36, 49.
42. Tisdall, F.: *Jour. Biol. Chem.*, 1922, 50, 329.
43. Clausen, S. W.: *Jour. Biol. Chem.*, 1921, 46, xviii.
44. Gram, H. C., and Norgaard, A.: *Jour. Biol. Chem.*, 1923, 56, 429.
45. Gettler, A. O., and Baker, W.: *Jour. Biol. Chem.*, 1916, 25, 211.
46. Bloor, W. R., and McPherson, D.: *Jour. Biol. Chem.*, 1917, 31, 79.
47. Folin, O., and Berglund, H.: *Jour. Biol. Chem.*, 1922, 51, 415.
48. Folin, O.: *Physiol. Rev.*, 1922, 2, 460.
49. van den Bergh, H.: *Der Gallenfarbstoff im Blute*, Leipzig, 1918.
50. Hansen, K. M.: *Acta. med. Scand.*, 1923, Suppl., 1.
51. Atchley, D. W., Loeb, R. F., Benedict, E. M., and Palmer, W. W.: *Arch. Int. Med.*, 1923, 31, 606.
52. Alder, A.: *Deutsch. Arch. f. klin. Med.*, 1918, 126, 61.
53. Linder, G. C., Lundsgaard, C., and Van Slyke, D. D.: Unpublished figures quoted by Salvesen, H., and Linder, G. C.: *Jour. Biol. Chem.*, 1923, 58, 617.
54. Gram, H. C.: *Arch. Int. Med.*, 1921, 28, 312.
55. Fåhræus, R.: *Acta. med. Scand.*, 1921, 55, 1.
56. Landolt and Bornstein-Roth: *Physikalisch Chemische Tabellen*, Berlin, 1912, p. 811.
57. Fraenckel, P.: *Ztschr. f. klin. Med.*, 1904, 52, 470.
58. Gram, H. C.: *Jour. Biol. Chem.*, 1924, 59, 33.
59. Gram, H. C., and Cullen, G. E.: *Jour. Biol. Chem.*, 1923, 57, 477.
60. Schmidt, C.: Quoted in Vierordt *Anatomische, physiologische und physikalisch chemische Tabellen zum Gebrauche für Mediziner* (1906).
61. Naegeli, O.: *Blutkrankheiten und Blutdiagnostik*, Berlin und Leipzig, 1919.
62. Gram, H. C.: Unpublished figures.
63. Keith, Rowntree and Geraghty: *Arch. Int. Med.*, 1915, 16, 547
64. Salvesen, H. A.: *Jour. Biol. Chem.*, 1919, 40, 109.
65. Smith, H. P., Arnold, H. R., and Whipple, G. H.: *Am. Jour. Physiol.*, 1921, 56.

LOW BACK PAIN AS SEEN IN AN ORTHOPEDIC CLINIC.

BY J. ALBERT KEY, M.D.,

ST. LOUIS.

(From the Orthopedic Clinic of the University Hospital, Baltimore.)

PAIN in the low back is a very common complaint among the adult patients who come to a general hospital for treatment. A large percentage of these patients eventually reach the orthopedic department, some of them immediately from the admitting desk, and others by transfer, after having been subjected to a variable amount of study and treatment in other departments.

Anatomically these cases can be divided into lesions of the lumbar and lumbosacral regions and lesions of the sacroiliac joints. Clinically the low back cases fall into three fairly well-defined groups:

1. Cases having definite injury or disease other than chronic arthritis.

2. Chronic arthritis involving the spine and pelvic joints.

3. Strains of the lumbosacral and sacroiliac joints.

The first group comprises tuberculosis of the spine or the sacroiliac joints, neoplasms, fractures (including Kummel's disease), dislocations, Charcot of the spine, acute arthritis of the spine, very rare pyogenic, typhoid, or syphilitic infection of the spine, myositis, contusions, atypical sprains and occasionally a cord or caudal tumor. The entire group makes up only from 5 to 10 per cent of the low back cases. A consideration of each of these conditions is not within the scope of this paper. It will be noted, however, that an early tuberculosis or neoplasm in this region may give signs and symptoms typical of a low back strain, and is usually diagnosed and treated as such until the destruction of bone or abscess makes the true condition evident. And rightly so, because it is better to treat one of these patients for a few weeks or months as a simple strain than to err on the other side and treat fifty strains as a more serious condition.

About 30 to 35 per cent of the low back cases have chronic arthritis, which is usually demonstrable in the roentgenogram. Chronic arthritis of the spine may be divided into:

1. Ankylosing.

2. Atrophic.

3. Hypertrophic.

The ankylosing arthritides of the spine are the spondylose rhizomeliques of Marie and Strumpell, characterized by very little or no pain and involvement of the great joints of the extremities, and the type of von Bechterew, characterized by root pains. The three types merge one into the other. All affect relatively young men, pursue a very chronic course and result in the poker back. The etiology is unknown and the treatment is unsatisfactory. Every effort should be made to prevent flexion deformity. Fortunately these cases are rare.

Atrophic arthritis (rheumatoid arthritis, proliferative arthritis, arthritis deformans) is characterized by fusiform swelling of the joints of the extremities, muscular atrophy, ankylosis with deformities, and bone atrophy. When the spine is involved the roentgenogram shows atrophy of the bone with partial collapse and flaring of the margins of the vertebral bodies. While atrophic arthritis is not uncommon, it is not a frequent cause of low back pain, because the disease is not prone to affect the spine. The etiology is unknown. Cases having low back pain should be given a corset or brace in connection with the treatment of the arthritis.

Hypertrophic arthritis (degenerative or osteoarthritis) is characterized by Heberden's nodes, thickening of the synovia of the involved joints, and the formation of bony spurs or lipping at the

osteocartilaginous margins. It is very prone to attack the spine, and is the great cause of arthritic conditions in the low back. The etiology is unknown. It occurs chiefly in the heavy type of the individual after middle life and tends to progress slowly. There is gradual stiffening, but not ankylosis, of the spine and other joints involved.

The pains in the low back suffered by the hypertrophic cases are, I believe, usually due to strains and not to the arthritis *per se*. The arthritis causes limitation of motion of the spine and renders it more susceptible to strain, but some of the most markedly hypertrophic spines that I have seen were encountered in the routine examination of patients, who stated that they had never been troubled with pain in the low back. Also I have seen a number of patients suffering from acute traumatic strain of the low back in whom the roentgenogram showed advanced hypertrophic changes in the spine, which must have taken a number of years to develop. Many of these patients stated that they had never had pain in the low back until the recent trauma. The indications in these cases are to diagnose the type of strain and then relieve the symptoms by appropriate treatment, as will be mentioned below in considering the back strains. Their body mechanics should be corrected and the back protected from strain, as it is more vulnerable than a normal spine, and recurrences are frequent. An attempt should be made to arrest the arthritis.

The strains of the low back comprise the great majority of the cases coming to the orthopedic clinic complaining of pain in this region. If we include the arthritics whose symptoms are due to strain about 80 to 85 per cent of the low back cases can be classed as strains.

Anatomically they can be divided into lumbosacral (80 to 85 per cent) and sacroiliac (15 to 20 per cent) strains. Clinically the lumbosacral strains can be subdivided into those of sudden onset with known cause, those of gradual onset without known cause and postural strains. The division of each subgroup into acute, recurrent and chronic is an arbitrary measure, because any of them may recur or become chronic. Any case in which the symptoms have persisted for more than four weeks may be considered chronic. Those cases in which a second attack has occurred from a slight cause may be classed as recurrent.

The lumbosacral strains of sudden onset are the most common of the low back strains (35 to 40 per cent of the group). They occur most often in men who are engaged in laborious occupations, though they may occur in women or men of sedentary habits. The patient can usually assign the onset of the pain to a definite cause which may be a severe trauma, such as a fall, wrench of the back or strain incurred in lifting a heavy weight, or it may be only a very minor cause, such as stooping over to pick up a pin from the

floor or getting into a bath-tub. The severity of the symptoms may be out of all proportion to the degree of the trauma. One of the most obstinate cases that I have ever encountered occurred in a strong, able-bodied man, aged thirty-five years, who, one morning, according to his custom, sat on the edge of the bed and leaned over to lace his shoes. All went well until he attempted to straighten up, then he had a severe sharp pain in his low back which caused him to fall to the floor in agony. He remained bedridden for two weeks and then began to hobble about. When I saw him two months later he was considerably disabled and walking with a cane.

As in the case cited above, the initial pain may be very severe and the patient totally disabled for the time being. But this is unusual. The usual history is that the patient had a "stitch" in his back while performing some unusual act and that the pain was not very severe and of short duration. He was conscious of his back from that time on, but paid little attention to it and continued with his work. That evening, or the next day, the pain reappeared and gradually increased in degree. The ultimate condition may be a very mild case in which the patient has a slight unilateral pain in the low back, which is produced by certain movements or positions, or he may be completely disabled by severe pain in the low back and leg.

The character and distribution of the pain are quite characteristic, though its degree and extent are variable. In general, the pain is sharp and lancinating, is aggravated by movement and with rest it may subside entirely or only a dull ache persist. These patients are usually able to assume a position in bed in which they are fairly comfortable, and once having obtained such a position are loath to move. As a rule, they are most comfortable when lying on the unaffected side, with the body, hips and knees moderately flexed, and a pillow between the knees. They have difficulty in turning over in bed at night, but, on the whole, have less pain at night than during the daytime.

In distribution the pain in the beginning is unilateral and most acute at a point just mesial to, and slightly below or above, the posterior-superior spine of the ilium. In the mild cases it remains in this region. In the more severe cases there is apt to be pain on the opposite side and in the lumbar muscles, but it is always most severe on the affected side in the region over the lumbosacral joint and ligaments. In the severe cases it is very common to have the pain appear some days later in the lower extremity on the affected side. This pain is always along the course of nerves whose fibers run in the lumbosacral cord. This gives a distribution in the buttocks along the superior gluteal, in the thigh along the sciatic and in the leg along the external popliteal to the back of the leg and external malleolus. Any or all of the above regions may be affected. These referred pains may be burning in character and in some cases

neurological examination may reveal areas of anesthesia or hyperesthesia. Occasionally the pain in the back entirely disappears, and only the sciatica persists. Many of these patients have had one or more similar attacks of varying severity.

On physical examination these patients are usually strong, healthy men. The objective findings vary directly with the severity of the symptoms. In a severe case the patient is unable to assume the erect posture, but stands with the body bent forward and listed away from the affected side—the so-called sciatic scoliosis. There is marked spasm of the muscles of the low back, the normal lumbar curve is obliterated and only very slight movements are permitted because of the severe pain. In the erect posture there is practically no movement in the low back. There is acute tenderness in the lumbosacral region of the affected side, and pressure here may cause pain in the distribution of the lumbosacral cord. There may be tenderness in the opposite lumbosacral region, in both erector spinæ, and in the buttock, posterior thigh, leg or external malleolus of the affected side. Deep abdominal palpation on the affected side may cause pain in the back.

Straight leg raising, full flexion of the hip, internal or external rotation of the flexed hips, hyperextension and Ely's maneuver cause acute pain, and are more limited on the affected side.

The above is a typical picture of a severe case. A mild case will show slight tenderness in the lumbosacral region of the affected side, slight limitation of motion in the low back, slight pain on bending forward, bending toward the affected side and upon straight leg raising. All gradations exist between the mild and very severe types mentioned above. It is to be noted that the physical signs may vary greatly from day to day, and twenty-four hours' rest in bed may produce a very marked change in the picture.

The postural strains of the lumbosacral region are more common in women. The pain is nearly always of gradual onset and without known cause, though in a few cases it follows an illness, a period of heavy work or a marked gain in weight. The condition is chronic, and most of the patients when seen by an orthopedist have been having trouble for some months or even years, not constantly, but from time to time, and especially after unusual physical or mental strain. A considerable number of the women with postural strains also have uterine displacements.

In a postural strain of the lumbosacral region the pain is usually worse at night. Many of these patients have very little pain during the day unless they do an unusual amount of work and get tired; but at night they are awakened by a dull aching pain in the low back, which is only relieved by sitting up in bed, getting up from bed, or a lumbar pillow. Or they may have the pain on getting up in the morning and it wears off in a short time. They start the day all tired out. The location of the pain is character-

istic. It is not referred down the thighs or legs, but is bilateral in the low back and most acute in the lumbosacral region. It may be more marked on one side. The pain is not sharp or burning, but is described as a dull ache, or it may be only a tired feeling.

On physical examination these patients may be of the heavy type with a sharp lumbar lordosis, the normal type with a moderate lumbar lordosis, or the slender type with a long lumbar curve. They may be weak and undernourished, or strong and muscular, or obese. In many of them the posture is very poor, in that they habitually stand with the head forward, shoulders drooped, chest flat, abdomen relaxed, lumbar spine hyperextended, body slumped and the body weight resting upon the heels with the feet pronated. All of them have the fault that they habitually stand with the lumbosacral region at or near the limit of hyperextension for the individual.

As in the lumbosacral strains of sudden onset, the objective findings vary directly with the severity of the symptoms. In the average case there is slight bilateral tenderness to deep pressure in the lumbosacral region, and pain here on hyperextension of the spine or of the hips and slight pain on bending forward. The movements of the spine are not limited. In a severe case there is also some spasm and limitation of motion in the low back and pain on straight leg raising and on lateral bending. In a mild case there may be no pain or tenderness at the time of examination, and all motions of the spine and hips are free and of normal range for the type of individual. Here the diagnosis is made by the history and physical findings which are negative, with the exception of the poor posture.

The above are the two clear-cut groups, and together comprise about 75 per cent of the cases of strain in the lumbosacral region. There is an intermediate group comprising about 25 per cent of these cases, which I term lumbosacral strain of gradual onset. The histories of these cases resemble those of the postural strains in that the pain is of gradual onset and without known cause, and in many of them it is worse at night in bed. Also in character the pain is usually described as a dull ache. On the other hand, the condition is more frequent in men, and the distribution of the pain is that characteristic of the lumbosacral strains of sudden onset, that is, the pain is unilateral in the low back and referred along the course of the fibers of the lumbosacral cord to the superior gluteal, sciatic and external popliteal nerves. As a class, the symptoms are much less than in the lumbosacral strains of sudden onset, though they may extend over a course of years, and at times be fairly acute and necessitate changes in occupation, though rarely ever cause complete disability.

On physical examination, if seen in an acute state, they have a flat back, with spasm in the lumbar muscles, and present the

typical picture of a lumbosacral strain of sudden onset and of moderate severity. In a mild case the poor posture is a prominent feature, but the limitation of motions and the pains elicited are those characteristic of lumbosacral strain of sudden onset rather than of postural strain.

The sacroiliac strains are, I believe, much less common than is generally supposed. In my experience about 1 in 5 of the low back strains has been classed as a sacroiliac strain. The onset may be acute, with or without trauma, or gradual. The pain is usually severe at night, especially upon turning over in bed, and may be a sharp pain or a dull ache. In others the pain is relieved by recumbency, but is acute on sitting up or walking. It may resemble that of the traumatic lumbosacral strain in distribution, but many of these patients also have pain in the inner side of the upper thigh and occasionally in the pubic region. The point of tenderness is characteristic in that it is located just below and lateral to the posterior-inferior spine, where the lower end of the sacroiliac joint can be palpated through the great sciatic ligament. It is to be remarked that the rest of this joint is protected posteriorly by the overhanging posterior border of the ilium, and tenderness in the neighborhood of the posterior-superior spine is not a sign of trouble in the sacroiliac joint. The same is true of tenderness upon deep abdominal palpation in the region lateral to the sacral promontory. Here the lesion may be either sacroiliac or lumbosacral.

Other than the location of the tenderness below the posterior-inferior spine, the characteristic sign in sacroiliac strain or disease is the ability of the examiner to elicit pain by putting strain upon the sacro-iliac joints without causing movement or strain in the lumbosacral region. This can be done by strongly compressing the anterior-superior spines of the ilia. Lateral compression of the spines strains the posteroinferior portion of the joints, and pressing the spines downward and outward, with the patient supine on a firm table, puts tension upon the anterosuperior portions of the sacroiliacs. If either of these maneuvers, when properly carried out, causes the pain of which the patient complains there is no question but that there is some difficulty in the sacroiliac joints. On rectal examination the lower portion of the joint can be palpated. Acute tenderness here is strong confirmatory evidence of strain or disease in the sacroiliacs. In all other respects the sacroiliac strain may give the clinical picture of a lumbosacral strain.

Roentgenograms are useful to determine the nature and extent of arthritis or other disease of the bone which may be present and to detect congenital anomalies in the lumbosacral region. Congenital anomalies are about five times as frequent in these low back cases as they are in an equal number of patients who do not have low back pain. When present they render the prognosis more grave, as such cases often respond poorly to treatment.

The pathology of these low back strains is unknown. I do not think that they are lesions of the muscles, but am inclined to the belief that the ones of sudden onset are true sprains, with tears of the ligaments or joint capsules. The referred pains are perhaps due to irritation of the fourth and fifth lumbar nerve roots by an exudate or by a synovitis of the adjacent joints. In the postural strains it is possible that the pain is due to irritation of the posterior sacrum caused by pressure of the articular processes of the last lumbar vertebra, which in hyperextension of the spine glide down over their facets to impinge upon the sacrum.

In treating these cases it is important to decide whether the lesion is lumbosacral or sacroiliac or both, and then direct the treatment to the involved region. An acute strain demands fixation and rest in bed, usually with sedatives. A firm strapping with adhesive plaster is often sufficient fixation if the patient will remain in bed for a few days. For a sacroiliac the strapping need not extend above the iliac crests, but for the lumbosacral it should extend up to the dorsolumbar region. Hot fomentations or other forms of local heat are often helpful. In bed a lumbar pillow and a pillow under the knees may be beneficial. For ambulatory treatment a narrow sacroiliac belt is used for the sacroiliac cases and a wide lumbosacral belt or low back brace is used for the lumbosacrals. In women the belt or brace can be incorporated in the corset or worn beneath it. Plaster jackets are seldom used, as it is extremely difficult to apply an ambulatory jacket which fixes either of these regions. The average case does well under the above treatment, but occasionally one meets a very resistant case in which prolonged rest in bed is necessary to effect a cure. Some of these difficult cases are helped by manipulation under full anesthesia; others are not. In some chronic sacroiliacs it may be necessary to arthrodesis the joint. This is best done by the Smith-Peterson method.

In the postural strains the acute symptoms demand support to the low back just as do the traumatic type of the lumbosacral strains. A permanent cure, however, is only obtained by correcting the poor posture. This is accomplished by a course of exercises directed to the correction of the body mechanics. The object of the orthopedist in treating these low back strains is first to relieve the symptoms, then to correct the mechanics of the low back and strengthen it by exercises until the patient is able to live a normal life, without any permanent supporting apparatus.

Summary. Low back pain and sciatica are frequent complaints among orthopedic patients. In the great majority of these cases the symptoms are due to strain in the lumbosacral or sacroiliac regions.

The lumbosacral strains are about four times as frequent as are those of the sacroiliac joints. Occasionally both regions are

involved. These low back strains may be due to trauma or to postural defects, and they may be acute or chronic. In patients beyond middle life hypertrophic arthritis of the spine is a frequent complication. The mode of onset, character and distribution of the pain, the location of the tenderness, the limitations of motion and the pain elicited by movement of the spines and hips are characteristic for each type of strain. There are, however, wide variations in the severity of the symptoms in strains which are essentially of the same type.

The diagnosis of the type of strain is made from the history and physical findings. A roentgenogram is of value in ruling out injury or disease of the bone, in determining the extent of arthritic changes, if present, and in detecting congenital anomalies of the spine. It does not differentiate between lumbosacral and sacroiliac strains. Sacroiliac luxation with slight displacement, demonstrable by the roentgen-ray, apparently does not occur. The characteristic symptoms and physical findings of each type of sprain are given above.

In the treatment it is important to make a definite diagnosis if possible and direct the therapy accordingly. The objects of treatment are relief from pain, resumption of normal activity and prevention of recurrence. Sedatives, rest in bed, support to the strained region, corrective exercises and physiotherapy are used in handling these cases. In arthritic cases the arthritis also should receive attention.

The prognosis is, as a rule, good. Chronic and recurring cases usually require a longer time for cure. Sacralization of the fifth lumbar vertebra makes the prognosis more grave, as these cases may be prolonged and difficult to relieve. Arthritis of the spine renders recurrence more likely.

THE THERAPEUTIC VALUE OF BLOOD TRANSFUSION.

WITH REPORT OF SIXTY-EIGHT CASES OF SEPSIS.

BY RUFUS E. STETSON, M.D.,

NEW YORK.

TEN years have passed since the development of blood transfusion from an uncertain, prolonged and delicate surgical operation, not without danger, to a quick, safe and comparatively simple procedure. During this time several methods of handling blood have been devised, and much has been said and written *pro* and *con* as regards their respective advantages.

Whole blood *versus* citrated blood has been the basis for more discussion than any other problem in this field of work, and for several years following its introduction the citrate method increased in popularity because of the greater ease of its accomplishment by untrained operators. Today the great majority of men prefer whole-blood methods because it is the safer method. It has been demonstrated beyond the shadow of a doubt that the use of citrated blood is accompanied by severe reactions in more than 50 per cent of the transfusions performed, and in some cases death has ensued as a result.

The cause or causes of posttransfusion reactions have been very thoroughly investigated. These vary from the lesser febrile reactions to the severe chill and high temperature with great prostration.

Novy and Dekrief¹ believe that the matrix of the poison anaphylactic toxin is in the plasma and serum of the blood, and they say that the disturbance which brings about the transformation of the matrix into poison is readily affected by the addition of almost any alien substance, even physiological salt solution. They also showed that toxic substances develop in blood on standing for a period of three minutes.

Drinker and Brittingham,² on the other hand, found that the blood platelets apparently have more to do with reactions than the serum, but that these early coagulation changes take place when the blood is kept out of its natural element for from three to five minutes, even in the presence of an anticoagulant, such as sodium citrate. They also showed that the mere addition of sodium citrate to blood causes slight abnormality of the red blood cells, increasing their fragility and tendency to hemolysis.

Unger³ confirmed and elaborated their findings as regards the effect of sodium citrate on red blood cells, and in his conclusion states that "Sodium citrate, even in the low percentage employed in a citrate transfusion, effects the red blood cells, rendering them more fragile, and the value of such blood to a patient suffering from a hemolytic disease, such as pernicious anemia, is lessened to that extent." Whether these toxic properties belong to the plasma, the red cells or the platelets, it is the consensus of opinion that the addition of any alien substance, even physiological salt solution to the blood, or the keeping of the blood out of its natural element for from three to five minutes, may activate these toxic properties.

Bernheim,⁴ of Baltimore, who had charge of the transfusion work in the A. E. F., where nothing but citrated blood was used, gave a fair and unbiased discussion of this subject. He says, "We must not be blind to the fact that the sodium-citrate-blood transfusion possesses certain obscure, but none the less inherent, features that are not only embarrassing to the physician, but most uncomfortable and even dangerous to the patient. Chills and fever and profound shock have never helped anyone, and to ignore the danger

of these sequelæ, merely to note their occurrence without vouchsafing a careful consideration of their eventualities, is little more than admitting a mind closed to certain embarrassing features connected with the procedure." And in conclusion he remarks: "I would not have you think for one moment that this is an attempt to belittle the value of the citrate transfusion—no one realizes better than I how much that has meant to the medical professional and to humanity at large—but it is necessary to recognize the fact that there are definite limitations to this method of giving blood, and that failure to observe these limitations has caused unnecessary loss of life. There should be in every community at least one man who is competent to carry out the whole-blood method, and physicians should learn to differentiate their cases so that they may take advantage of this man's skill and give their charges that chance for life for which they come to him."

Dr. Bernheim is a man of wide experience not only in general surgery, but one who has performed many blood transfusions himself, and who, in June, 1917, read a paper before the American Medical Association advocating the general adoption of the citrate method. It is, therefore, particularly gratifying when such a man comes out with such conclusive support of the opinion long held by Lindeman, Unger and other workers in this field, including the author.

My preference for the syringe cannula method is based on the fact that it is the most flexible and quickest and injures the blood as little as any other method, and with a little training is the easiest to accomplish. Three things are necessary to this operation as to any other, that is, perfect instruments, accurate knowledge of the technic in all its details and practice. The first two essentials are not difficult of attainment, and a very moderate amount of practice will enable one to accomplish the operation successfully. It is less dependent on mechanical factors than any other method because there is less apparatus. The blood is out of its natural element only about ten to fifteen seconds, or just the length of time it takes to transfer a single syringe-ful, no matter whether you give 20 cc or 2 liters, as I have done on more than one occasion. One can give as much or as little blood as the condition of the patient may justify during the operation without wasting any blood, or the procedure may be halted at any time to observe the effect on patient or donor and then resumed without any break in technic. Two assistants, one trained in the technic of withdrawing blood from the donor and one untrained, for the washing of the syringes are desirable but not essential, as I have accomplished the entire procedure unassisted. The special cannulæ, three to five 20-cc record syringes and four basins of sterile normal salt solution is all the apparatus necessary.

Indications for Transfusion. Transfusion is coming to be used more and more as a therapeutic measure, but much progress

remains to be made in the profession at large in getting away from the idea that it is a measure to be used only as a last resort. It is useful in the following conditions.

Hemorrhage.

Hemorrhage, acute and chronic.

Hemorrhage of the newborn.

Purpura.

Hemophilia.

Anemias.

Secondary anemia	{	Pregnancy or puerperium.	{	Empyema.
		Chronic surgical cases		Burns.
		Malnutrition.		Traumatic.

Pernicious anemia.

von Jakschs' anemia.

Sepsis.

Acute or chronic	{	Osteomyelitis.	{	Mastoid sinus or jugular
		Multiple arthritis.		thrombosis.
		Multiple abscesses.		Tonsillectomy.
		Postoperative		
		Puerperal.		

Toxemia.

Pneumonia.

Typhoid.

Scarlet fever.

Nephritis.

Acute infections.

Jaundice.

To reduce clotting-time of blood if operative procedure is indicated.

To overcome toxemia.

Miscellaneous.

Gas-poisoning.

Drug addiction.

Shock in operative procedures.

We have employed it successfully in typhoid fever to combat the severe toxemias as well as hemorrhage, and I have had 2 cases of encephalitis complicating scarlet fever, both of which recovered—1 after six transfusions and the other after two. Both had severe convulsions, controlled only by chloroform, and were extremely ill; both showed marked and steady improvement as soon as the transfusions were started.

I no longer advise transfusions in acute lymphatic leukemia, as it is a very temporary help, and life is rarely prolonged more than a few weeks.

Transfusion for Hemorrhage. The results in hemorrhage are naturally the most uniformly successful and often the most dramatic. Obstetrical and gynecological conditions furnish the largest proportion of acute hemorrhage cases. It has long been my contention that every expectant mother should have her blood group determined in order to save valuable and perhaps vital time in case of need. I recall 4 fairly recent cases which will serve as good examples of this group. Three of them occurred in the practice of the same man, a surgeon of Jersey City.

The first case was a woman, of middle age, who had carried a slow-growing fibroid for several years without any symptoms except the gradually increasing size of the abdomen. She finally came to the physician last summer for excessive bleeding. The tumor by that time had reached an enormous size, filling the whole lower abdominal cavity, and it was decided to try to reduce it in size by radium before operating. Treatment was accordingly started, and marked reduction in the size of the tumor was soon noted, but the bleeding got worse instead of better, and I was called to transfuse her on July 29, 1922. No blood count was done, but she was extremely anemic and very weak. She was given 1000 cc of blood, and, while there was immediate improvement, the bleeding failed to stop, and she was given 1200 cc of blood on September 9. A few more days' observation, with no check in the bleeding, made it evident that operative interference was imperative; consequently, I went over on September 15 with two donors and, after giving 650 cc of blood, a hysterectomy was performed and, though greatly reduced in size, the fibroid then removed was as large as a good-sized pumpkin. Immediately following the operation the patient was given 500 cc more blood from the second donor, a total of 1150 cc, and she made a quick, uneventful and complete recovery.

The second case was one of incomplete abortion, with severe hemorrhage. A consultant was called, and the patient was hurried to a hospital; meanwhile a specimen of blood for grouping was sent to me. No time was wasted, but when I arrived the woman was semicomatose and in very poor condition. She was given 1000 cc of blood, and when we finished she was laughing and talking, and went through a curettage the next morning without any trouble.

The third case was in a woman, aged forty-one years, with no previous history of bleeding. She had had two or three miscarriages but no children. At her last period two or three weeks previous she had bled only one day instead of several as usual. Her bleeding began suddenly and was quite profuse. A physician was called in consultation and, while a definite diagnosis could not be made, he suspected a ruptured ectopic and felt that an exploratory laparotomy was indicated. Her condition by that time made her an extremely poor operative risk, so I was asked to come prepared to transfuse before and after operation as I had done in the

first case. She was given 800 cc and as soon as the needle was withdrawn from her vein the anesthetic was started. A hysterectomy was performed, and it was discovered that all her trouble was from a small submucous fibroid. She stood the operation very well, and after receiving 500 cc more of blood was sent back to the ward in excellent condition.

The lives of all 3 of these women were undoubtedly saved by transfusion, but I mention them particularly because of the fact that not only was severe hemorrhage successfully combated, but also because extremely poor operative risks were thereby transformed into very good risks. The surgeon's nerves were saved considerable wear and tear and his reputation enhanced.

The fourth case is an argument in favor of blood-typing of all pregnant women, and an example of the danger of transfusing without doing tests. The case was that of a young healthy woman of the poorer class. It was during the sixth month of her first pregnancy, during which she probably had had very little medical attention. At any rate she was brought into the Manhattan Maternity one evening as an emergency. She was found to be a case of placenta previa, and bleeding profusely. The uterus was emptied as expeditiously as possible, but not, of course, without considerable additional loss of blood, which left her in a very precarious condition. I was called and found her almost pulseless, semicomatose and apparently dying. The patient's mother was the only relative present, and it is interesting to note that the daughter bore a striking physical resemblance to her. It seemed like a case where we were justified in transfusing without a moment's delay; consequently, preparations were quickly made, and the transfusion started with the mother as donor. Only two syringefuls of blood, 40 cc, had been introduced when the patient evinced signs of distress, drawing up her knees and groaning, followed by vomiting and extreme cyanosis, which with her pallor gave her a positively green appearance. I immediately stopped the transfusion and gave her 750 cc of physiological salt solution. She rallied temporarily but died in about two hours, before tests could be completed and the proper donor secured. Before starting the transfusion I had taken specimens from both mother and daughter, and subsequent tests proved them to belong to totally different blood groups.

Transfusion in Anemias. There is a peculiar type of anemia which sometimes occurs during pregnancy or the puerperium, perhaps due to the strain put upon the hemopoietic system or it may be an endocrine disturbance; however that may be, it cannot be differentiated from pernicious anemia so far as the blood-picture goes, but is permanently corrected by transfusion.

In the past three and a half years I have had the opportunity to treat 92 cases of pernicious anemia. In all 294 transfusions were performed on these 92 patients, from one to twenty-six transfusions being given to the individual case. The total quantity of blood

transfused was 326,420 cc or $326\frac{1}{2}$ liters, from 650 cc to 2300 cc (2 donors) being given at a time—an average of over 1100 cc for each transfusion.

In 8 of the patients the course of the disease was not appreciably affected, death occurring within one to six weeks. One of these patients had two transfusions and 7 had but one. In 2 patients I have no record as to how long their improvement lasted. In 56 patients it was possible to prolong life from three months to two years and to relieve them of their most distressing symptoms, though without definite remissions. One of these patients in a year and ten months required twenty-six transfusions, a total of $30\frac{1}{2}$ liters of blood, but during the major part of that time he was kept fairly comfortable and active enough to settle his important business affairs. Life cannot be measured in dollars and cents, but, as in this case, even a few months' prolongation of life may be of distinct economic value to those intimately concerned. In the remaining 23 cases one or more remissions have occurred. The shortest, three months' duration; the longest in this series, two years, and still continuing. Four are having their second remission, having now gone sixteen, ten, nine and eight months respectively.

It seems evident that no other therapeutic measure has the power and efficacy that transfusion of unmodified blood has in treating pernicious anemia. It is indicated whenever the hemoglobin reaches 35 or 40 per cent and whenever distressing symptoms arise, even when occurring at a much higher level. Amounts of 1000 cc or over of unmodified blood give the best results, for by using large amounts we obtain the maximum improvement both in the blood and in the general condition of the patient and also give them a much longer interval between transfusions.

Transfusion is always indicated in idiopathic purpura hemorrhagica, but my experience has been that it is very likely to go on to a fatal termination in spite of everything that may be done. It is an absolute, though not permanent, specific in hemophilia. In bleeding of the newborn the hemorrhage is not only controlled, but the effect is lasting.

Most of the von Jakschs' anemias do very well after transfusion.

We have 2 patients with Hodgkin's disease still living that did very well. In both instances the febrile crises, occurring every ten days or so, were checked, and a definite remission induced in 1 patient, while the other has at least been kept alive and is being given radium and roentgen-ray therapy.

Transfusion in Sepsis. We see a good deal of chronic empyema and osteomyelitis on the Children's Surgical Service at Bellevue Hospital, and these cases are apt to be in extremely poor condition when referred to me. They have a marked secondary anemia, and their wounds respond very sluggishly to treatment. They may be quite toxic from absorption, and often their appetite and digestion are poor. It is most gratifying to see how well these children do with

an occasional transfusion. Their secondary anemia is overcome, their appetite and digestion immediately improve and in a surprisingly short time their wounds begin a healthy granulation. The danger of intercurrent infections is also lessened and their convalescence greatly shortened.

This is also true of the bad traumatic cases and some of the burn cases that have a long drawn-out convalescence.

Some of the bad malnutrition cases on the infants' service are also saved by transfusion.

The following is a partial report of my work on sepsis. It seems to me that the results in this condition are of the greatest importance because of the seriousness of the condition we have to combat. In the past we had to depend almost wholly on the natural strength and resistance of the patient, and even today, in spite of vaccines, serums and colloids, we would be just about as helpless as ever in the face of acute sepsis were it not for blood transfusion.

Lindeman was the first to prove this, and it was his good work that first convinced me of the efficacy of the measure. I know there has been some debate on this matter and that it has not proved successful in all hands. We received no heaven-sent inspiration on how to use blood therapy, but through experience we have learned how to apply the measure to the best advantage and have succeeded in cutting down the mortality in sepsis by a substantial percentage.

In using blood therapy to combat sepsis we have a two-edged weapon: The power it has to overcome the secondary anemia and build up the general condition of the patient and the direct bactericidal action of the fresh blood on the infecting organism. The latter factor is, of course, the more variable, depending on the virulence and character of the organism, the focus of infection and the phagocytic power of the blood employed, but I have observed steady diminution in the number of colonies and final sterilization of the blood stream in a sufficient number of cases to convince me that normal blood has a very real value as a bactericidal agent.

The use of immunized donors should theoretically be much more effective, but in the cases I have observed the results did not seem to justify this belief, and the elements entering into the production of immunity either actively in the patient or passively in the case of the donor are so complex and so little understood that we cannot argue convincingly from a laboratory point of view. We are forced, as indeed is so often the case, to take the clinical results as our ultimate, deciding factor. It is only fair to say, however, that the difficulties in the way of immunizing donors in time to be of any use in acute sepsis has made it impossible to employ this method in a conclusive number of cases.

I have treated by blood transfusion about 100 cases of undoubted sepsis. The group of 68 cases that are included in this report were not selected but were taken indiscriminately. Many of these cases

were from the wards of Bellevue Hospital, and were much poorer material to work with in the beginning than one usually encounters in private practice.

The cases will be studied first from a bacteriological viewpoint and then according to the clinical diagnosis.

Thirty-nine of the cases showed positive blood cultures (Chart I). *Streptococcus hemolyticus* occurred in 19 instances, with 10 recoveries and 9 deaths. Of the 9 patients that died pneumonia killed 4 and meningitis developed in 2.

CHART I.

Patients.	Diagnosis.	Blood cultures positive for.	No. of trans-fusions.	Result.
1	Malignant endocarditis	<i>Streptococcus viridans</i>	6	Died.
2	Malignant endocarditis	<i>Streptococcus viridans</i>	7	Died.
3	Malignant endocarditis	<i>Streptococcus viridans</i>	2	Died.
4	Malignant endocarditis	<i>Streptococcus viridans</i>	1	Died.
5	Malignant endocarditis	<i>Streptococcus viridans</i>	1	Died.
6	Malignant endocarditis	<i>Staphylococcus aureus</i>	1	Died.
7	Malignant endocarditis	<i>Streptococcus viridans</i>	7	Died.
8	Mastoid with sinus and jugular thrombosis	<i>Streptococcus hemolyticus</i>	2	Recovered.
9	Mastoid with sinus and jugular thrombosis	<i>Streptococcus hemolyticus</i>	3	Recovered.
10	Mastoid, sinus thrombosis, pneumonia, empyema, acute nephritis	<i>Streptococcus hemolyticus</i>	5	Recovered.
11	Mastoid, sinus thrombosis, pneumonia, empyema	<i>Streptococcus hemolyticus</i>	3	Recovered.
12	Mastoid, sinus thrombosis	<i>Streptococcus hemolyticus</i>	2	Recovered.
13	Mastoid, sinus thrombosis	<i>Streptococcus hemolyticus</i>	2	Recovered.
14	Mastoid, sinus thrombosis	<i>Streptococcus hemolyticus</i>	3	Recovered.
15	Mastoid, jugular thrombosis	<i>Streptococcus hemolyticus</i>	2	Recovered.
16	Mastoid, jugular thrombosis	<i>Streptococcus hemolyticus</i>	3	Recovered.
17	Mastoid, jugular thrombosis	<i>Streptococcus hemolyticus</i>	1	Died.
18	Mastoid, sinus thrombosis	<i>Streptococcus hemolyticus</i>	2	Died.
19	Mastoid, sinus thrombosis	<i>Streptococcus hemolyticus</i>	6	Died of pneumonia.
20	Mastoid, sinus thrombosis	<i>Streptococcus hemolyticus</i>	4	Died of pneumonia.
21	Scarlet fever, mastoid and sinus thrombosis	<i>Streptococcus hemolyticus</i>	7	Died of pneumonia.
22	Mastoid, sinus thrombosis	<i>Streptococcus hemolyticus</i>	4	Died of meningitis.
23	Postpartum sepsis and osteomyelitis	<i>Streptococcus hemolyticus</i>	2	Recovered.
24	General sepsis with initial focus in cervical glands	<i>Streptococcus hemolyticus</i>	4	Died.
25	General sepsis with initial focus in cervical glands	<i>Streptococcus hemolyticus</i>	9	Died of meningitis.

Patients.	Diagnosis.	Blood cultures positive for.	No. of transfusions.	Result.
26	Postpartum sepsis, pneumonia, gangrene of lung	Streptococcus hemolyticus	4	Died of pneumonia.
27	Post abortion sepsis	Streptococcus viridans	8	Died.
28	Sepsis following tonsillectomy	Streptococcus viridans	2	Recovered.
29	Acute multiple osteomyelitis, multiple abscesses, pyopericarditis	Staphylococcus aureus	16	Died.
30	Acute multiple osteomyelitis	Staphylococcus aureus	11	Recovered.
31	Cellulitis of face	Staphylococcus aureus	1	Died, moribund time of transfusion.
32	Postpartum sepsis	Staphylococcus aureus	1	Died (moribund).
33	Cellulitis of face	Staphylococcus aureus	5	Died.
34	Cellulitis of leg	Staphylococcus aureus	2	Died.
35	Maxillary sinusitis	Staphylococcus aureus	2	Recovered.
36	Post operative appendix	Staphylococcus aureus	1	Died (moribund).
37	Postpartum sepsis	Staphylococcus aureus	2	Died.
38	Frontal sinusitis brain abscess	Staphylococcus aureus	4	Died, meningitis.
39	Acute osteomyelitis	Staphylococcus aureus	2	Recovered.

Streptococcus viridans occurred in 8 cases, 6 of them being malignant endocarditis and fatal in termination. The seventh occurred in a baby, after tonsillectomy, who recovered after two transfusions. The eighth patient had a postpartum sepsis, and died.

Staphylococcus aureus which, contrary to popular belief, is, in my experience the deadliest of the infecting organisms in general sepsis, occurred in 12 patients, 9 of whom died and only 3 recovered. Of the 9 deaths, however, 3 were moribund at the time of the first transfusion, and 1 had an acute endocarditis, so that in at least 4 cases we never had a chance, and a fairer ratio would be 3 recoveries to 5 deaths. The total figures in this group show 14 recoveries to 25 deaths, or 36 per cent of recoveries, with a mortality of 64 per cent.

	Patients.	Recoveries.	Per cent.	Deaths.	No.
Streptococcus hemolyticus	19	10	55.0	Pneumonia	4
				Meningitis	3
				Sepsis	2
Streptococcus viridans	8	1	12.5	Malignant endocarditis	6
				Puerperal sepsis	1
				Moribund	3
				Malignant endocarditis	1
Staphylococcus aureus	12	3	25.0	Pyopericarditis	1
				Cellulitis	2
				Puerperal sepsis	1
				Meningitis	1
Total	39	14	36.0		25

If, however, we subtract, as I feel we have a right to do, the 3 moribund patients and the 7 patients with malignant endocarditis

it leaves 14 recoveries to 15 deaths, or practically a mortality of only 51 per cent.

Considered from a diagnostic viewpoint, there were in the streptococcus hemolytic group 14 patients with mastoid and sinus or jugular thrombosis or both, and of these 9 recovered and 5 died. In 2 of the patients that recovered we carried them through a complicating pneumonia and empyema. Of the 5 we lost 2 died of pneumonia and 1 of meningitis. In the remaining 5 cases of *Streptococcus hemolyticus* 2 started from glands of the neck. In 2 patients with puerperal sepsis the *Streptococcus hemolyticus* was isolated and 1 recovered, though she had a complicating osteomyelitis. The other died, after we thought she was safe, of gangrene of the lung following a pneumonia. The fifth patient had a bad suppurative arthritis of the knee which we lost. It is interesting to note that of the *Streptococcus hemolyticus* 73 per cent were in mastoid patients, and that of these more than 64 per cent recovered. The excellent results in this type of case are due no doubt to the fact that the surgeon is able to remove the septic thrombus from vein or sinus, but only in observing the majority of these cases clinically can one appreciate the part blood therapy plays in their recovery.

The *Streptococcus viridans* was, with 2 exceptions, confined to the malignant endocarditis cases (6 in all), and so far as my experience goes they invariably die. One exception previously mentioned was in the case of the baby following tonsillectomy, which recovered. The other followed abortion. We transfused her eight times but lost her, though it may be permissible to add that the conditions under which we were working were not of the best.

In its malignant form *Staphylococcus aureus* can kill more quickly and resist treatment more stubbornly than any of the common organisms with which I have come in contact. Undoubtedly there are more superficial localized infections from this organism than any other, but fortunately its tendency is to remain localized and clear up readily under treatment. Of the 12 patients in which this organism was isolated 3 started as a cellulitis—2 of the face and 1 of the leg—following the scratching or picking of an insignificant looking pustule. All 3 died, 1 being moribund at time of transfusion. Three were suffering from a multiple osteomyelitis. One required eleven transfusions but recovered, the second recovered after two transfusions and the third we lost after sixteen transfusions from a pyopericarditis.*

Two patients with puerperal sepsis showed staphylococcus and both died. Two started as sinusitis: One a maxillary, which recovered; the other frontal, which died of meningitis following a successful operation for abscess of the brain. One case developed

* Since this paper was written we have had a similar case of multiple osteomyelitis with positive blood culture for *Staphylococcus aureus* and complicating pyopericarditis which recovered after nine transfusions.

staphylococcus septicemia following an appendectomy and died, and the last was apparently an acute endocarditis, though no autopsy was performed.

In 29 of these 68 cases either no blood culture was obtained or the cultures were sterile, but no cases have been included that were not unanimously considered sepsis by all who saw them. Exception might be made of 2 cases of gas-bacillus infection following amputation of the leg after traumatic injury in both instances. One patient recovered and the other died of pneumonia after four transfusions and when the stump had regained a healthy granulating appearance and all crepitation had disappeared from the surrounding tissues. At any rate their inclusion does not affect the ratio of our recoveries and deaths (Chart II).

CHART II.—SHOWING CASES IN WHICH THE INFECTING ORGANISM WAS NOT RECOVERED FROM THE BLOOD.

Diagnosis.	No. of cases.	Recoveries.	Deaths.
Mastoid with sinus or jugular thrombosis	7	3	4 2 died of pneumonia.
Postabortion or puerperal sepsis	14	9	5 { 2 moribund at time of transfusion; 2 died of pneumonia
Empyema	1	1	0
Influenza	1	1	0
Osteomyelitis	2	2	0
Suppurative arthritis	1	0	1
Endocarditis	1	0	1
Gas bacillus infection	2	1	1 Died of pneumonia.
	<hr/> 29	<hr/> 17	<hr/> 12

There were 7 patients with mastoid and sinus or jugular thrombosis. Three of them recovered and 4 died, 2 from pneumonia.

There were 14 patients with postabortion or puerperal sepsis, with 9 recoveries and 5 deaths. Of the 5 that died 2 were moribund when transfused and 2 died of pneumonia. One of the latter had run a normal temperature for four days previous to onset of pneumonia.

Of the 6 remaining patients 1 with an empyema recovered; 1 starting with an influenza infection, with particularly bad tonsils, also recovered; 1 patient with osteomyelitis, and 1 with osteomyelitis combined with suppurative arthritis, recovered; 1 patient with a suppurative arthritis died; 1 died from endocarditis.

Our figures in this group then show 17 recoveries and 12 deaths, and of that 12, 2 were moribund and 1 had an endocarditis.

Our total figures are as follows:

Diagnosis.	Total.	Deaths.	Recoveries.
Mastoid cases	22	10	12
Malignant endocarditis	7	7	0
Postabortion and puerperal sepsis	19	9	10
Osteomyelitis	5	1	4
Miscellaneous foci	15	10	5
	<hr/> 68	<hr/> 37	<hr/> 31

This gives out of 68 patients 31 recoveries and 37 deaths, but of these 37 deaths 7 patients were suffering from malignant endocarditis and 4 others were moribund at time of transfusion. I feel that we had a fighting chance in only 57 patients, giving a ratio of 31 recoveries to 26 deaths, and of these 26 7 died of a complicating pneumonia and 5 of meningitis.

Conclusion. This report of our work on sepsis is not complete, but even this limited number of patients seems to me to show the efficacy of blood transfusion in this condition. I feel that a great many patients could be saved if transfusion were started early and given every forty-eight hours until the blood cultures became sterile and the clinical improvement sufficiently marked to make it safe to stop. In most instances it is best to give only 500 to 600 cc of blood—less in children. I usually withdraw from the patient one-half to two-thirds of the amount to be given just before starting the transfusion.

It is evident also from this report that the most dreaded complications are pneumonia and meningitis. Escaping these, and given a fighting chance, blood transfusion offers any patient with septicemia at least a 50 per cent chance for recovery.

BIBLIOGRAPHY.

1. Novy, F. G., and Dekrief, P. H.: Jour. Am. Med. Assn., 1917, 68, 1524.
2. Drinker, C. K., and Brittingham, H. H.: Arch. Int. Med., 1919, 23, 133.
3. Unger, L. J.: Jour. Am. Med. Assn., 1921, 77, 2107.
4. Bernheim, B. M.: Jour. Am. Med. Assn., 1921, 77, 275.

THE INTERESTING BEHAVIOR OF TUBERCULOUS GUINEA-PIGS UNDER PARATHYROID AND CALCIUM ADMINIS- TRATION; A PRELIMINARY REPORT.

BY P. S. PELOUZE, M.D.,

AND

RANDLE C. ROSENBERGER, M.D.,

PHILADELPHIA.

WHEN this work was started, in 1914,¹ it was rather generally felt that in the tuberculous individual there was a lessened calcium tissue content and that this was one of the underlying factors in susceptibility to the disease. This belief has been advanced and contradicted up to the present time, and though it is claimed by some recent investigators² that there is no such deficiency, count-

¹ Proceedings Philadelphia Pathological Society, 1915; 36, 29; 1916, 37-38, 29.

² Marvel and Wells: Am. Rev. Tuberc., 1923, 7, 1.

less clinicians still urge the use of calcium in the treatment of the disease. Were we to rebuild the theory upon which this work was done to conform to present-day knowledge we would be prone to agree with their contention, but would feel that, though the cells of the body might be constantly bathed in fluids of normal calcium content, it was not even then proved that they were able to make proper use of the obtainable calcium. In other words, though you offered them the food they needed, you did not prove that it became a part of their intracellular chemistry.

Let us state in the beginning that the basis of our work was purely theoretical, and that we are herein briefly reporting the results of our investigations suggested by these theories. One theory was that there was some derangement of calcium metabolism, as the result of which it was not properly taken up and utilized by the tissue cells. It made little difference for our work whether this applied to all of the cells of the body or only to those that entered into the destruction of the tubercle bacillus.

It should be said that these thoughts came to one of us as the result of rather closely following the work of Russell,³ based upon the lime-salt starvation theory. It will be recalled that this investigator, after an enormous amount of clinical work, summed up his experiences with the opinion that there was a systemic need for calcium, but for some reason there was a marked difference between calcium administration and calcium metabolism; that, though the substance was fed in large or small quantities, tuberculous subjects evidently lacked something that was necessary to cause it to enter into true intracellular chemistry.

Some years later it occurred to one of us that, as the parathyroid glands were evidently the controllers of calcium metabolism, the underlying factor might be a hypoparathyroidism; that in tuberculosis there was a lessened parathyroid secretion which prevented the absorbed calcium from taking part in the true action for which it was needed.

There has, of course, been much controversy upon the true function of these small glands, but their action in calcium metabolism seems well established. A recent editorial⁴ crystallizes our knowledge upon the subject and leaves little doubt as to their importance in this regard.

With these two thoughts in mind it was determined to see if the administration of these two substances, separately and together, would in any way influence the course of tuberculosis in guinea-pigs. The results of our investigations herein given seem to warrant a continuation of this work, as well as to furnish sufficient justification for a thorough clinical investigation of the problem.

³ Russell, John F.: *Med. Record*, 1909, **76**, 889 and 1021; 1911, **80**, 12.

Van Gieson, I. and Lynah H. L.: *Med. Record*, 1912, **81**, 883.

⁴ *Jour. Am. Med. Assn.*, 1923, **31**, 663.

Stress of other work has taken both of us away from the subject for some time, and it is largely with the hope of stimulating such a clinical study that this purely preliminary report is made. It is our feeling that the work as it stands is only highly suggestive, but that in it somewhere possibly rests a truth of the greatest value to mankind. We can conceive of no danger to the patient in carrying out such clinical investigations. A very brief experience with the substances in 9 advanced cases of pulmonary tuberculosis in man showed such a striking change from the steady weight losses they were experiencing as to make us feel it a matter worthy of study by those better able to weigh the results than ourselves.

In carrying out our work we first took 7 guinea-pigs and placed them in separate cages in a quiet well-aired room. They were given all they would eat, and weighed once a week. When they began to show a steady weight gain they were deemed ready for inoculation. Due regard was paid to each factor that could interfere with the value of the experiments, so that they can be said to be influenced adversely by nothing but a minimum of excitement. One who carries out weight experiments upon these little animals will early observe that such a trifling thing as putting them into strange cages, or moving the cages to which they are accustomed to other parts of the same room, will cause them to lose weight. The same applies to excitement or handling, particularly those infected with tuberculosis.

As it was our desire to produce a tuberculosis that would more nearly approach the disease as generally encountered in human beings, we chose a greatly attenuated strain of the human tubercle bacillus. The particular strain used was a descendant of the Saranac culture of Baldwin, known as "R. I.," which had been subcultured in the laboratory of one of us (R. C. R.) since 1904. This strain was the one which Gardner¹ found to be of such low virulence that it produces "Lesions which progress to caseation, and that this caseation, together with the accompanying proliferation of fixed tissue cells, is then absorbed. The healing process is one of resolution, of which no trace remains at the site of the former lesion." Gardner's observations were upon the pulmonary lesions following inhalation inoculation. It is our observation that this course is rarely encountered following intraperitoneal inoculation. In fact, with the large doses used by us many massive lesions occurred, and when we doubled our dose, as we did in one group, the animals were overwhelmed by the infection. It is probably the case that the course of the lesions in untreated pigs is governed by the size of the dose and the varying susceptibility of the animals.

In our first two series of 7 animals each an intraperitoneal inoculation of 1 cc of a heavy normal salt suspension of the organism was

¹ Am. Rev. Tuberc., 1922, 6, 163.

given. The medication was suspended in sterile distilled water, placed upon bread and given once daily as follows:

1. Tuberculous control.
2. Tuberculous, 1 gr. calcium lactate.
3. Tuberculous, $\frac{1}{80}$ gr. parathyroid substance (Armour & Co.).
4. Tuberculous, 1 gr. calcium and $\frac{1}{80}$ gr. parathyroid.
5. Non-tuberculous, 1 gr. calcium.
6. Non-tuberculous, $\frac{1}{80}$ gr. parathyroid.
7. Non-tuberculous, 1 gr. calcium and $\frac{1}{80}$ gr. parathyroid.

This was continued for a period of three and a half months. It was early noticed that the tuberculous pigs, with the exception of tuberculous control, ate more food than the well pigs, and it was shown by actual food-weighing that the tuberculous pig on both preparations consumed far more food than any of the others. Singularly enough, this was the case in each series of experiments. From our observations it would seem that one could safely say that a tuberculous pig receiving both drugs will eat more than any of his fellows in a like series, and that he will even eat more food than a normal animal living under like conditions.

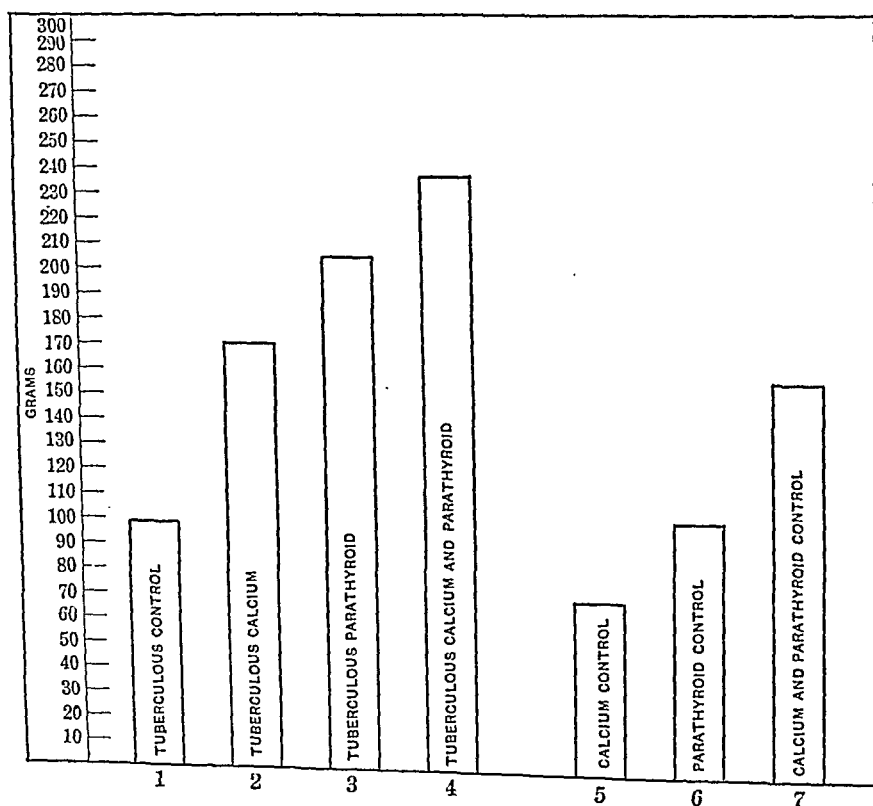


CHART I

In Chart I will be seen the result of our first series as regards ultimate weight gains. These results are remarkable from several standpoints, and gave much encouragement for further investiga-

tions. It will be seen that the tuberculous pigs gained more than the non-tuberculous, but that the order of gain was consistent in both.⁶

There is much of a suggestive nature in the autopsy notes regarding the extent of the macroscopical evidences of tuberculosis. They are briefly as follows:

1. Tuberculous control: Very large caseous mass in the omentum, two lesions 0.5 cm. in diameter in the liver and one in the anterior wall of the stomach. (These lesions were larger than the combined lesions of the other three pigs.)

2. Tuberculous calcium: Several small caseous masses in the omentum, two very small caseous nodules in the liver and adhesions between the liver and the belly wall.

3. Tuberculous parathyroid: Four small caseous masses in the omentum and several small nodules in the liver.

4. Tuberculous calcium and parathyroid: Small caseous button in belly wall at site of inoculation, a minute nodule in the liver with an adhesion between it and the small bowel. (All much smaller than in either of the others.)

Because of these results the experiment was duplicated in every particular with the results as seen in Chart II. With the exception of the tuberculous parathyroid pig there is a marked uniformity in the two results. This animal apparently enjoyed little native resistance to the disease, as he showed massive lesions, eventually dying of pneumonia. Pneumonia likewise killed the non-tuberculous calcium pig. The most remarkable feature was the weight gain of the tuberculous parathyroid and calcium animal, a gain which exceeded 270 gm.

From these two series it was apparent that there was a fairly constant ratio of weight gain upon the different types of medication in well pigs, and that there was little necessity of continuing the work upon these controls.

At the end of this series it was decided not to sacrifice the animals, but to see if the well pig upon the two drugs had been given any real resistance to the disease. It was accordingly inoculated as the others had been and allowed to go without further medication. With it were continued the tuberculous control and the tuberculous calcium and parathyroid pig without further medication. The weight gains in nineteen-week periods will be seen in Chart III. It is extremely interesting that at autopsy the first-mentioned of these three (the former non-tuberculous parathyroid and calcium) showed no macroscopical evidences of tuberculosis. For this we could not account at the time, but it is possibly in conformity with Gardner's findings. If so it is the only evidence in the group of the entire

⁶ For the average weight gains of well guinea-pigs based upon 3634 investigations, the reader is referred to Wood's Reference Handbook of the Medical Sciences, 2d ed. 4, 421.

disappearance of lesions. Whether or not its course of medication prior to inoculation was the cause of its entire recovery from the large dose of tubercle bacilli, it is of course impossible to say. It is, however, worthy of remark that this was the only animal in which it occurred.

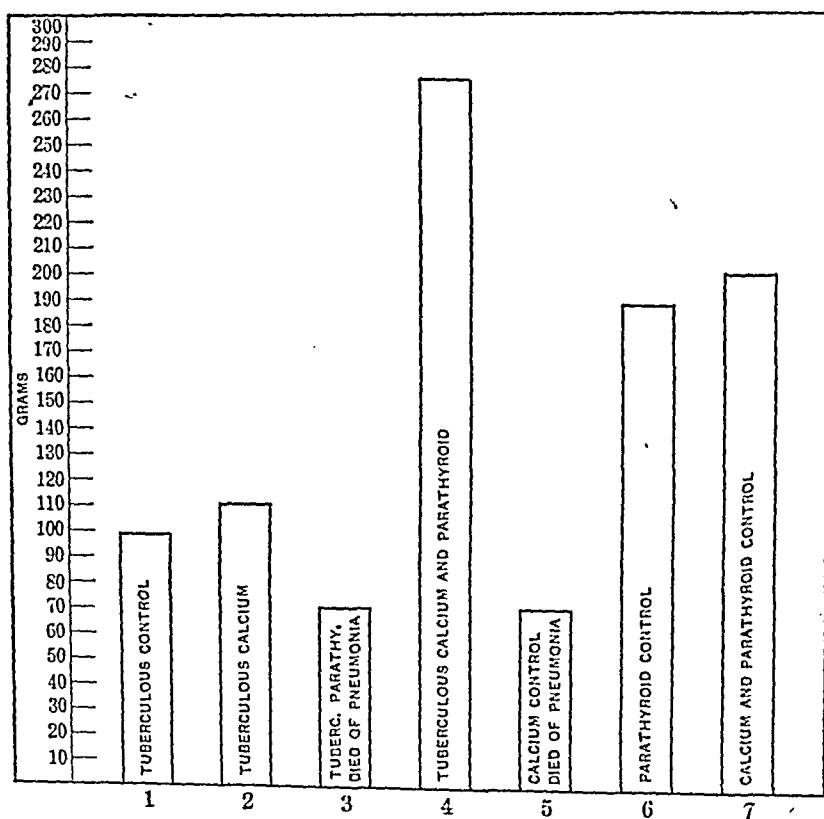


CHART II

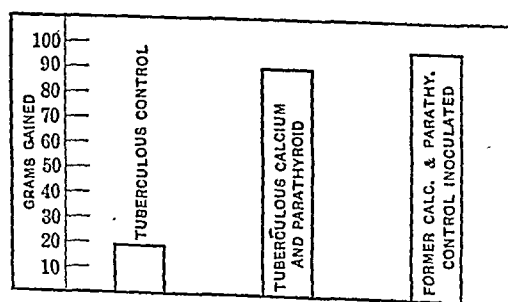


CHART III

Another larger series, consisting of 3 tuberculous controls and 20 tuberculous parathyroid and calcium pigs, was then started. Shortly thereafter an epidemic of diarrhea broke out among them and carried off so many that the group was discontinued. They were carried along for such a short time as to be of little value, but it is worthy of note that at the last weighing preceding the epidemic

the average gain of the control pigs was 72 gm. as against 92 gm. of the tuberculous animals receiving both substances.

Some time after this a fourth series was started in the private laboratory of one of us (P. S. P.), as it was not convenient to repeat it where the others were done. These animals were unwisely given a dose twice as great (2 cc) as that of the former ones. Due to this overwhelming dose, the initial weight losses were greater and more prolonged than in either of the other series. These animals died in a short while, but their weight trend, as seen in Chart IV, is somewhat suggestive of our former findings.

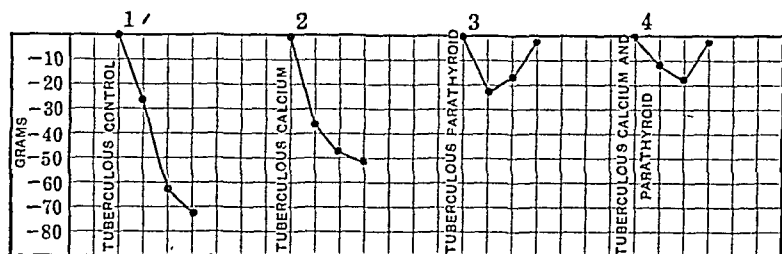


CHART IV

As has been stated, it was our hope to continue this work upon a larger and more conclusive scale, but stress of other duties has prevented our doing so. We do not feel that we have proved that our theories are facts, but we do feel that much of an extremely suggestive nature has been brought out and that, considering the vagaries of the laboratory guinea-pigs, there has been striking uniformity in the findings. This, together with a very brief and limited clinical trial, makes us feel no hesitancy in making a plea for a more extended trial under the auspices of those doing clinical work in this disease.

Summary. 1. The theory upon which these experiments were based is that in the tuberculous and those predisposed to tuberculosis there is a hypoparathyroidism which curtails the final stages of calcium metabolism, as the result of which the calcium does not enter properly into true intracellular chemistry.

2. Tuberculous and non-tuberculous guinea-pigs were given calcium and parathyroid substance separately and combined and, while it is not felt that the thesis is in any sense proved, it is deemed that the results are of such a suggestive nature as to warrant this preliminary report.

3. The results so far can be briefly summarized as follows:

(a) The lesions were greater in the tuberculous control and less marked in the calcium-fed animals. In those given parathyroid and in those getting both substances the lesions were still less marked.

(b) The weight gains bore an inverse relation to the size of the

lesions, as would be expected, and were much greater in those upon the combined medication.

(c) The tuberculous animals receiving both drugs ate far more than either of the others and even more than normal pigs under like conditions.

(d) It would seem that if one wished to make a guinea-pig gain enormously while taking calcium and parathyroid he should inoculate him with tuberculosis.

(e) The results in all of these series are as consistent as one who has handled laboratory guinea-pigs very much would expect, and make it highly suggestive that similar results might be obtained in certain classes of patients with tuberculosis.

4. It is our hope that others will take up this work in human beings for in it somewhere, we feel, is the answer to a problem that has baffled us all and that tuberculin has never answered.

THE SELECTIVE ACTION OF THE SUPRARENAL CORTEX SECRETION ON MESOTHELIAL TISSUES.

BY ROBERT C. MOEHLIG, M.D.,

DETROIT, MICH.

(From the Department of Internal Medicine, Harper Hospital, Detroit, Mich.)

In this article the clinical and embryological evidence supporting the following conclusions will be presented:

1. The suprarenal cortex secretion has a selective action on mesothelial tissues.

2. The normal development and continuous normal functioning of the sexual glands and skeletal muscular system is dependent upon the normal functioning of the suprarenal cortex.

3. Anterior cerebral defects include the pituitary gland, which in turn are accompanied by suprarenal cortex defects.

In a previous communication I⁴³ made the observation that the individual endocrine glands exerted a selective action on certain tissues, and that this selective action was specific and correlated with the germ layer from which the tissue in question was derived.

The work on the suprarenal cortex in recent years has strengthened my opinion that the cortex secretion is essential for the development and normal functioning of the mesothelial tissues. Since the suprarenal cortex and the reproductive organs have the same embryological origin, and since tumors of the cortex are frequently associated with sex anomalies, it was natural for workers in this field to try to demonstrate a functional relationship between these tissues. So far as I am aware no one has advanced the idea that the suprarenal cortex has a selective action on mesothelial cells.

To simulate diseased conditions of the suprarenal cortex by experimental methods proves a difficult task for several reasons, the principal ones being the anatomical fact that in higher mammals the cortex and medulla are so closely related and the apparently established physiological fact that the cortex is essential to life. No one can belittle the valuable contributions of the research worker in the field of endocrinology. For every statement made he demands an experimental demonstration. The clinician finds it easier to speculate and draw conclusions based upon clinical findings. But the clinician sees the lesions produced by so-called natural consequences, whereas the research worker sees lesions produced by means only simulating actual diseased conditions. This is particularly true in Addison's disease. The pigmentation of Addison's disease has not been successfully produced in animals by suprarenal extirpation. It is, of course, evident that the combined efforts of research worker and clinician are necessary for the advancement of endocrinology.

The interrelationship of the endocrine glands has made the problem a most difficult one. It is my opinion that the problem can be made easier by utilizing known embryological facts. In addition to the experimental data, it would seem worth while to study the clinical physiology of the suprarenal cortex in its relation to the embryological origin of certain tissues, such as mesothelial tissue.

It was stated in the aforementioned communication that pathological changes in the pituitary, *per se*, constantly produce changes in the bones, cartilage, fat, bloodvessels, lymph glands, smooth muscles and other mesodermal structures. Recently Bauer, in studying the pathological changes in osteogenesis imperfecta noted "That all mesenchymal tissues, such as bone, cartilage, vessels, hemopoietic organs, were affected. Chondrodystrophy and the progressive muscular dystrophies are other examples of affections limited to mesodermal structures. Schaeffer, independently of Bauer, found analogous affections of the ectoderm in amaurotic idiocy and hereditary spinal spastic paralysis."

The present article deals only with the suprarenal cortex and the selective action of its secretion on mesothelial tissues. The somatic and splanchnic layers of the mesoderm form on their celomic surfaces a single layer of squamous cells, termed the mesothelium. The mesothelium is, therefore, a differentiated part of the mesoderm. From the mesothelium are derived the following tissues: 1. Peritoneum. 2. Pleura. 3. Pericardium. 4. Urogenitals: (a) Wolffian body; (b) kidney (non-mesenchymal portion); (c) ovary; (d) oviduct: (1) Uterus (non-mesenchymal portion); (2) vagina. 5. Striated muscles: (a) skeletal; (b) cardiac.

The suprarenal medulla and cortex have different embryonic origins—the former is derived from the sympathochromophil tissue of the ectoderm and the latter from the celomic epithelium of the

mesoderm. The cortical cells appear before those of the medulla and the cortex is already a large body before it receives the anlage of the medulla.

A study of the literature, and particularly that of recent years, convinces one that the suprarenal cortex, and not the medulla, is essential to life. Houssay and Lewis³¹ established certain definite facts from their experiments with suprarenalectomy. Some of these facts are:

"1. Double suprarenalectomy is fatal in most species.

"2. Dogs survive extirpation of all chromophil tissue contained in the suprarenals, when the remaining cortex is in good state.

"3. If the remaining cortex is removed the animals die, as after double suprarenalectomy.

"4. Dogs without the suprarenal medulla maintain their function normally.

"5. No abnormal pigmentation or asthenia is observed."

Biedl,⁷ after an extensive study of the literature and analysis of the reported experiments on suprarenalectomy, as well as having performed a number himself, concluded that the suprarenal cortex is essential to life. Those animals which survived total extirpation of both suprarenals were shown to have accessory suprarenal tissue composed of cortical substance. Wheeler and Vincent⁵⁵ destroyed all the medullary tissue of the suprarenals by cauterization and left the cortical substance intact. Those animals in which considerable damage had been done to the cortex died. Hartman²⁸ is of the opinion that of the two suprarenal tissues, medulla and cortex, the latter is the more important and is essential to life. Crowe and Wislocki,¹⁶ from their experiments on dogs, conclude that the suprarenal glands are vital organs, and it is probably the cortex which is essential to life, an opinion shared by the majority of workers.

Relation of the Suprarenal Cortex to Mesothelial Tissues. In order to avoid monotonous repetition, I will treat collectively the changes found in mesothelial tissues in those conditions which produce hypofunction and hyperfunction of the suprarenal glands, and also those changes produced by feeding experiments.

Hypofunction. Marshall and Davis⁴² have shown that the excretory power of the kidney is very much reduced in animals in which the suprarenals had been removed. As this occurs despite the fact that the blood-pressure remains normal and the animals are in good condition, it would indicate that the suprarenals play an important part in renal activity. Bevier and Shevky⁶ have also shown that extirpation of the suprarenals in rabbits decreases the excretion of urea. Cow¹⁵ demonstrated that there was a direct vascular connection between the kidney and suprarenal, but this has not been demonstrated in man. Bremer⁸ claims that the renal, suprarenal and sex-gland arteries are derived from an early periaortic plexus.

Addison's disease produces a hypoplastic or atrophic state of the

suprarenals. The kidneys are small and atrophic and chronic interstitial nephritis is frequent. Kyrle³⁵ found deficient spermatogenesis and degenerative changes in the interstitial glands in this disease. Impotency and amenorrhea are usually present. The extreme degree of muscular asthenia is one of the outstanding features of this disease. The cardiac muscle shares in this asthenia and is atrophic, thus accounting for the weak heart action and possibly the low blood-pressure.* Loss of epinephrin, through destruction of the medulla, cannot explain the low blood-pressure, because investigations have shown that circulatory blood does not contain enough epinephrin to influence the blood-pressure.

Biedl's extirpation experiments on the fish species, skates and rays, give very strong support to the opinion that the suprarenal cortex has a selective action on the skeletal musculature. In this species of fish the suprarenal medulla and cortex are anatomically separate. Excision of the interrenal (cortex) tissue produced striking symptoms. These, which began, as a rule, seven to eight days after operation, consisted of lessened movements and lifelessness. The spontaneous swimming around in the tanks became decidedly less. Fourteen to eighteen days after operation the muscular asthenia became so pronounced that the fish were unable to swim. They lay practically the whole day in a corner of the tank and took no nourishment. Stimuli failed to produce a reaction. Three weeks after operation they died with general prostration.

Elliott and Tuckett,²¹ from their observations, concluded that the cortical portion has a definite relation to the skeletal musculature. Elliott, speaking of the muscle tone control says:

"The striped skeletal muscles form a homogenous group which is continually under a tonic influence. This tone is for the most part derived from direct nervous impulses, but the diseased state of myasthenia gravis proves that the tone is not altogether supplied from the central nervous system. Myasthenia might, in the skeletal muscles, correspond to the state of Addison's disease in the bloodvessels. But this is only a surmise. I have tried in vain to discover an active substance in the muscle plates of striped muscles. Professor Herring was also disappointed when he examined for this purpose the electrical organs of the skate, which are exaggerated motor plates."

Elliott and Tuckett noted that the suprarenals increase with the development of the skeletal muscles, the increase affecting mainly the cortex. They also found that the cortex parallels the weight, whereas the medulla remains stationary. Severe exhaustion is always associated with hemorrhagic dilatation of the blood spaces in the cortex. In the kitten a movement of fat from the outer to

* That the cardiac muscle atrophy may be due to the long-standing illness is a possibility, but this is unlikely when we compare it with the cardiac muscle found in other diseases of longer standing than Addison's.

the inner third of the cortex was produced by exhaustion. In a dog that had journeyed thirty miles all cortical cells were found to be vacuolized to a degree only seen in the fat-bearing zone of the outer third of the suprarenal cortex. In a study of the suprarenals of other animals it was found that the fowl medulla is very large and is three times that of the guinea-pig, which has comparatively the largest suprarenal cortex. It would seem that the lower the animal in the scale of vertebrates, the larger is the stock of chromaphil tissue.

The above-mentioned authors conclude that the following substances are evidence of secretory activity: (1) A fatty and (2) a doubly refractive substance; (3) brown granules of the cortex; (4) the chromaphil substance of the medulla.

The first two are nearly related. The doubly refractive substance increases with rest, when the fat becomes less abundant. In phases of exhaustion it vanishes and the fat spreads all over the cortex. But neither are essential factors in a generalized type of cortical activity, for neither appears in the sheep. The brown granules appear characteristically and plentifully in the guinea-pig and over a restricted area in the ornithorhyncus. They accumulate with rest and disappear very early in exhaustion; the cytoplasm of the cells in which they have been stored then develops fat. Exhaustion of the medulla is shown to be a progressive thinning of the substance, which stains yellow with potassium bichromate. In states of extreme exhaustion this stain finally vanishes.

It is true that epinephrin delays the onset of fatigue in skeletal muscles, but this is given off only in emergency periods, and my point is that the cortex secretion maintains the *normal* skeletal metabolism. Panella,⁴⁶ Cannon and Nice,¹² and Gruber²⁵⁻²⁶ have demonstrated that epinephrin delays the onset of fatigue in skeletal muscles. Some (Hoskins, Gunning and Berry³⁰) believe that the beneficial effect following epinephrin injections in muscle fatigue are due to circulatory improvement. Gruber believes that the improvement is not due to circulatory increase, but to overcoming fatigue products; for he demonstrated that epinephrin is beneficial even after denervation of the muscles, with the muscles in a state of dilatation. He likewise showed that epinephrin combats the effects produced artificially by injections of lactic acid and phosphate. Cannon's well-known work seems to prove that epinephrin is only present in the circulation during periods of great stress—the so-called emergency theory. There is some question, however, whether epinephrin represents the true principle of medullary secretion.

Bardier and Bonne,³ in studying the modifications produced in the structure of the suprarenals by tetanization of the muscles, found that these affected the cortex of the gland, not the medulla. Vincent says "We do not know why its [cortex] removal causes

death, but it is possible that this is due to some defect in muscular metabolism."

Of lesser importance are the changes found in the peritoneum, pleura and pericardium in diseases of the suprarenals. Just what changes these tissues should show in diseases of the suprarenals is questionable. In Addison's disease there usually exists, and more particularly in the end stages of the disease the picture of peritonitis. The abdomen is retracted and the abdominal walls are tense, producing what Ebstein¹⁹ termed "pseudoperitonitis." The peritoneum is smooth and glistening. Pleural and pericardial adhesions are a frequent finding.

In acute and chronic infections the lipoid content of the suprarenal cortex disappears, whereas in chronic circulatory diseases it increases. Chronic nephritis falls in the latter group and, therefore, it is of interest to note MacCallum's³⁸ statement: "Rather curious is the frequent occurrence of pericarditis in the terminal stages of chronic nephritis, and in those cases it is generally difficult to find any bacteria."

Hyperfunction. Hypernephroma of a hyperfunctionating type produces marked changes in the urogenital and skeletal muscle systems. Female infants with this type of hypernephroma menstruate, and are unusually muscular and strong. Infant boys have premature development of the genitalia, and are equal in size and strength to boys at the age of fifteen and sixteen years. The literature contains many reports of cases of this nature. Glynn²⁴ gave a very good summary of the reported cases at the time his paper was written. He is certain that there is an intimate connection between sex characteristics and the suprarenal cortex. Bullock and Sequeira,¹¹ Apert,² Quinby,⁴⁸ Jump,³² Strauch⁵¹ and many others have reported cases. It is not necessary to go into detail regarding these cases, as the association between suprarenal cortex tumors and precocious sexuality is well known.

Pseudohermaphroditism is frequent associated with hyperplasia of the suprarenal cortex. Marchand,⁴⁰ who first reported such autopsy findings, found colossal hyperplasia of the cortex associated with a large accessory suprarenal.

Jump³² says that at present we are justified in believing virilism and hirsutism are caused by increased functioning of the suprarenal cortex, varying in degree and due in some instances to hypernephromatous growth of the suprarenal cortex.

Vincent⁵⁴ concludes that there is considerable evidence which indicates that the suprarenal cortex has important functions in connection with the development of the reproductive organs. He says that tumors of the cortex are frequently, though not constantly associated with sex abnormalities. This is true, but tumors are not all of the same type and do not necessarily increase cortex function; in fact they may lessen its function.

Hyperplastic changes are found in the suprarenal cortex during rut or in pregnancy (Guieyesse,²⁷ Stoerk and von Haberer⁵²). Aichel¹ noted that the suprarenals were large when the sex organs were well developed and during the breeding season. Stilling⁵⁰ also noted suprarenal enlargement in male rabbits during breeding season. Leupold³⁶ found a close relationship existing between the suprarenals and testicles. He says that when the suprarenals contain much fat the quantity of fat in the testicles is also high. The testicles contain less cholesterol than do the suprarenals, and when cholesterol diminishes in the testicles and the suprarenals it is generally first decreased in the testicles. He believes that this proves that the suprarenals have a higher function than the testicles. Podvissotsky⁴⁷ and Mulon⁴⁵ called attention to the resemblance of the ovarian cortical cells to the suprarenal cortex. Mulon believes that the corpus luteum of pregnancy is a temporary suprarenal cortex. Elliott²⁰ says: "There is reason to believe that interrenal tissue is embedded in the sex gland itself, giving rise to lutein cells of the ovary or the interstitial cells of the testis. By the latter cells are determined the sexual character of the individual."

Serdioukov⁴⁹ carried out a series of experiments on pregnant and non-pregnant cats. These experiments showed that there exists a functional interdependence between the suprarenal cortex, the parenchyma of the corpus luteum and the interstitial gland of the ovary. They have a vicarious relationship. This conclusion is verified by the lipoid character of each of these tissues. Marassini,⁴¹ Cecca¹³ and others found an increase in weight of the suprarenals following castration. This affected only the cortex. The vicarious relationship may account for the cortical hyperplasia.

Feeding experiments with suprarenal substance also gives evidence of a relationship between cortex and sexual glands; van Herwerden,⁵³ using 1 or 2 mg. of dried suprarenal cortex tissue added to 10 to 15 cc of hay infusion containing *Daphnia pulex*, stimulated growth and accelerated the maturing and reproductive processes. Similar stimulation of growth was observed with the eggs of the snail and with frog larvæ. R. G. and A. D. Hoskins,²⁹ experimenting with white rats, fed them desiccated suprarenal substance. Hypertrophy of the testes and ovaries was noted in several of the younger animals, although some of the controls also showed a similar hypertrophy. Vincent believes the latter experiments would prove more valuable if cortical substance alone were employed for feeding; furthermore the process of desiccation probably removes the important "lipoids" which might contain physiologically active substances.

Recently in a series of cases in which I thought suprarenal cortex secretion might be beneficial, viz, amenorrhea, muscular asthenia and 1 case of Addison's disease, I gave five hundred injections of a

suprarenal preparation.* This preparation consisted of an acetone soluble solution of suprarenal substance after the epinephrin had been extracted. It was, therefore, a suprarenal residue of the whole gland and was not absolutely epinephrin-free. The results were entirely negative.

In this same series of cases I fed over a thousand 5 gr. capsules of desiccated suprarenal substance. Beef suprarenal glands were cut in half and the cortex and medulla were grossly dissected from one another. The cortical portion was desiccated and prepared in the usual manner. Here, too, the results were absolutely negative. The case of Addison's disease showed a rather remarkable improvement of five weeks' duration. But as Addison's disease, like exophthalmic goiter, has periods of remission, and as no benefit was noted in the other cases, this improvement can hardly be ascribed to the cortex-feeding. Shortly afterward, despite the daily administration of 60 gr. to 80 gr. doses of the cortex substance, the patient died of exhaustion. Autopsy revealed atrophic suprarenals. No tuberculosis was present.

For reasons which will form the subject of another paper, it is my opinion that disease of the pituitary gland is always accompanied by disease of the suprarenal cortex. Primary lesions in the pituitary produce pathological changes in the suprarenal cortex. Briefly stated for the purpose of the present article, it is maintained that the posterior lobe of the pituitary gland has a selective action on mesenchymal tissues; of which the suprarenal cortex is a part.† The mesenchyme and mesothelium are differentiated parts of the primitive mesoderm, and are closely related. How closely related these tissues are is evidenced by the work of Lewis,³⁷ who says:

"The migratory mesenchymal cells in cultures of the embryonic chick heart show all stages of transformation from the bipolar and multipolar reticular cells to the flat mesothelial forms: One can actually observe this change in form. Such mesothelial cells seem to differ from the mesenchymal cells only in form and not in structure, indicating that mesothelium is to be considered not as a tissue differentiated from the mesenchyme, but merely as a change or transformation in form."

Further evidence of their close relationship is shown by Clarke's¹⁴ experiments, which indicate that mesothelium can be formed from the mesenchyme, even in adult life.

If the posterior lobe of the pituitary has this selective action on mesenchymal tissues, such as bone, smooth muscle, connective

* This suprarenal material was kindly furnished me by the Research Department of Parke, Davis & Co.

† The well-known action of pituitrin on smooth muscle and bloodvessels is an evident clinical demonstration of its effect on mesenchymal tissues. From a speculative standpoint it might be theorized that the beneficial action of pituitrin in diabetes insipidus is due to its effect on the collecting tubules of the kidney, which are mesenchymal in origin.

tissues and bloodvessels; then it would be reasonable to suppose that the great increase in the weight of the bones, such as seen in acromegaly, requires a commensurate enlargement of striated muscle to control them. This is accomplished by suprarenal cortex hyperplasia. Falta²² says that suprarenal cortex hyperplasia is a very frequent finding in acromegaly.

It is apparent, therefore, that disease of the posterior lobe of the pituitary gland will produce pathological changes not alone in mesenchymal tissues, but through accompanying cortical changes in mesothelial tissues as well.

It is of interest that injections of posterior lobe extract produce a hypertrophy of the suprarenal cortex. Sexual function in the early stage of acromegaly is increased. Great increase of muscular power in this stage is very apparent, these individuals posing in circuses as "strong men." The kidneys are enormously enlarged and show a true hyperplasia. In 2 cases of acromegaly Fischer²³ found immense suprarenals, affecting especially the cortex. Delille¹⁸ likewise found this condition.

In hypoplastic states of the pituitary gland, hypoplasia of the suprarenal cortex is found. Total aplasia of the suprarenals is found in anencephaly, hemicephaly and other failures of brain development. Ziegler⁵⁷ cites several cases of anencephaly and hemicephaly associated with aplasia of the suprarenals. Zander,⁵⁶ Morgagni⁴⁴ and Czerny¹⁷ also report brain defects associated with suprarenal aplasia. Kaufmann³³ says that the suprarenals and cerebrum have been placed in functional and genetic relationship. According to him, in hemicephaly and anencephaly the suprarenals are almost constantly found to be hypoplastic in greater or lesser degree. He quotes Zander to the effect that the suprarenals are hypoplastic only in defects of the anterior portion of the brain. From this it follows that the anterior cerebral defects include the pituitary gland, which would, therefore, account for the suprarenal cortex defect. Recently Büchler¹⁰ tried to show a relationship between the pituitary and midbrain. Kohn³⁴ believes that suprarenal hypoplasia is secondary to changes in the hypophysis in anencephalic fetuses. Defects are found in the infundibulum and pars nervosa. The epithelial portion also show changes. There is scarcity of oxyphil cells and large basophil cells. Browne⁹ studied 5 anencephalic fetuses. He was struck by the constancy with which the thymus, suprarenals and ovaries were involved in association with the anencephaly. Commenting on Browne's work, a leading article in the *British Medical Journal* (1920, 2, 828) says: "The most rigorous search on the basis cranii of his anencephalic fetuses showed absolutely no trace of a pituitary gland. The syndrome, consisting of protruding tongue and eyeballs, nasal aquilinity, obesity, thymus hyperplasia, suprarenal and genital hypoplasia and stunted growth of body and limbs, agrees in the main with the

features of what are called hypopituitarism and apituitarism."* Barlow,⁴ however, examined 4 anencephalic fetuses. He found no difficulty in locating the anterior portion of the pituitary gland. In none of them was there a real attempt at the formation of a sella turcica. He states that from the discovery of the anterior segment of the pituitary gland in 4 successive typical examples, it may be concluded that the other features of the condition are not due to apituitarism.

There can be no doubt, I believe, that defects of anterior portion of the brain involve the pituitary gland. But there also can be no doubt that the pituitary gland is not the etiological factor in the cerebral defect as Browne would prove, but is merely involved through its anatomical location. In Zander's 43 cases of anencephaly the suprarenal cortex defect was present only in those cases which included the anterior portion of the brain. We may conclude that in those cases of anencephaly which include the pituitary gland the suprarenal cortex is hypoplastic. It is apparent that some anencephalics do not have apituitarism and, therefore, do not show the syndrome completely. Barlow's 4 cases were probably of this type.

Mackenzie³⁹ says:

"The aplasia or hypoplasia of the glands [suprarenals] in conditions of anencephaly and similar defects of the central nervous system is well authenticated and is of much greater interest on account of the fact that a proper explanation of the changes in these conditions may ultimately lead us to a clearer view of the functions of the cortical portion of the glands."

The embryological idea expressed in this paper would seem to offer an explanation for a better understanding of the endocrine problem.

Summary. A review of clinical and embryological evidence supports the following conclusions:

1. The suprarenal cortex secretion has a selective action on the mesothelial tissues.
2. The normal development and continuous normal functioning of the sexual glands and skeletal muscular system is dependent upon the normal functioning of the suprarenal cortex.
3. Anterior cerebral defects include the pituitary gland, which in turn are accompanied by suprarenal cortex defects.

BIBLIOGRAPHY.

1. Aichel, O.: Vergleichende Entwicklungsgeschichte und Stammesgeschichte der Nebennieren, *Arch. f. mikr. Anat.*, 1900, 56, 27.
2. Apert, E.: La portion corticale de la capsule surrénale, ses relations physiologiques et pathologiques avec le cerveau et les glands genitales, *Presse méd.*, 1911, 19, 865.

* "Nature's Teratological Experiments".

3. Bardier, E., and Bonne: Note sur les modifications produites dans la structure des surrénales par la tétanisation musculaire, *Jour. de l'anat. et de la physiol.*, 1903, 39, 296.
4. Barlow, D. L.: Apituitarism and the Anencephalic Syndrome, *Brit. Med. Jour.*, 1923, 1, 15.
5. Bauer, K. H.: Hereditary Constitutional Affections, *Klin. Wehnschr.*, 1923, 2, 624; Abstract, *Jour. Am. Med. Assn.*, 1923, 81, 172.
6. Bevier, G., and Shevsky, A. E.: Urea Excretion after Suprarenalectomy, *Am. Jour. Physiol.*, 1919, 40, 191.
7. Biedl, A.: Innere Sekretion, Urban and Schwarzenberg, Berlin, 1910, pp. 141-147.
8. Bremer, J. L. (quoted by Dawson, A. B., and Reis, J. H.): An Anomalous Arterial Supply to Suprarenal, Kidney and Ovary, *Anat. Rec.*, 1922, 23, 161.
9. Browne, F. J.: The Anencephalic Syndrome in its Relation to Apituitarism, *Edinburgh Med. Jour.*, 1920, 25, 296.
10. Büchler, Paul: Hypophysis and Interbrain, *Ztschr. f. d. Neurol u. Psychiat.*, 1922, 80, 331.
11. Bullock, W., and Sequeira, J.: On the Relation of the Suprarenal Capsules to the Sexual Organs, *Tr. Path. Soc. London*, 1905, 56, 189.
12. Cannon, W. B., and Nice, L. B.: The Effect of Adrenal Secretion on Muscular Fatigue, *Am. Jour. Physiol.*, 1913, 32, 44.
13. Cecca, R.: Ovar und Nebenniere, *Soc. med. chir. de Boulogne*, March, 1904.
14. Clarke, W. C.: Experimental Mesothelium, *Anat. Rec.*, 1916, 10, 301.
15. Cow, D.: The Suprarenal Bodies and Diuresis, *Jour. Physiol.*, London, 1914, 48, 443.
16. Crowe, S. J., and Wislocki, G. B.: Abdominal Chromaffin Body in Dogs, *Bull. Johns Hopkins Hosp.*, 1922, 33, 377.
17. Czerny, A.: Hydrocephalus und Hypoplasie der Nebennieren, *Centralbl. f. allg. path. Anat.*, 1899, 10, 281.
18. Delille, A.: l'Hypophyse et la modification hypophysaire, 1909, G. Steinheil, Paris, 352 pp.
19. Ebstein, W.: Peritonitisartiger Symptomencomplex in Endstadium der Addison'schen Krankheit, *Deutsch. med. Wehnschr.*, 1897, 23, 729.
20. Elliott, T. R.: The Adrenal Glands, *Brit. Med. Jour.*, 1914, 1, 1393.
21. Elliott, T. R., and Tuckett, I.: Cortex and Medulla in the Suprarenal Glands, *Jour. Physiol.*, London, 1906, 24, 332.
22. Falta, W., and Meyers, M. K.: The Ductless Glandular Diseases, Philadelphia, P. Blakiston's Son & Co., 1916, p. 351.
23. Fischer, B.: Hypophysis, Akromegalie und Fettsucht, Bergmann, Weisbaden, 1910.
24. Glynn, E. E.: The Adrenal Cortex, its Rests and Tumors; its Relation to the Other Ductless Glands and Especially to Sex, *Quart. Jour. Med.*, 1911-1912, 5, 157.
25. Gruber, C. M.: The Significance of Epinephrin in Muscular Activity, *Endocrinol.*, 1919, 3, 145.
26. Gruber, C. M.: Further Studies of the Effect of Adrenalin upon the Blood Flow in Muscles, *Am. Jour. Physiol.*, 1918, 47, 185.
27. Guieyette, A.: La capsule surrénale chez la femelle du cobaye en gestation, *Compt. rend. Soc. de biol.*, 1899, 51, 898.
28. Hartman, F. A.: Endocrinology and Metabolism, New York, D. Appleton & Co., 1922, 2, 105, 127, 237, 257.
29. Hoskins, R. G., and Hoskins, A. D.: The Effects of Suprarenal Feeding, *Arch. Int. Med.*, 1916, 17, 584.
30. Hoskins, R. G., Gunning, R. E. L., and Berry, E. L.: Effects of Adrenin on the Distribution of the Blood, *Am. Jour. Physiol.*, 1916, 41, 513.
31. Houssay, B. A., and Lewis, J. T.: The Relative Importance to Life of Cortex and Medulla of the Adrenal Glands, *Am. Jour. Physiol.*, 1923, 64, 512.
32. Jump, Henry D.: Clinical Syndromes Due to Suprarenal Diseases, *Endocrinol. and Metab.*, New York, D. Appleton & Co., 1922, 2, 345.
33. Kaufmann, E.: Spezielle Pathologische Anatomie, Berlin, George Reimer, 5 Auflage, 1909, p. 772.
34. Kohn, A.: Anenzephalie und Nebenniere, *Deutsch. med. Wehnschr.*, 1922, 48, 1666 (Secretary's Report, Verein deutsch. Aerzte, June, 1922).
35. Kyrle, J.: Ueber die Hypoplasie der Hoden in Jugendalter und ihre Bedeutung für das weitere Schicksal der Keimdrüsen, *Wien. klin. Wehnschr.*, 1920, 33, 185.

36. Leupold, E.: Beziehungen zwischen Nebennieren und männlichen Keimdrüsen, Jena, 1920, Gustav Fischer, 62 pp.
37. Lewis, Warren H.: Mesenchyme and Mesothelium, Jour. Exper. Med., 1923, 38, 257.
38. MacCallum, R. G.: A Text-book of Pathology, 2d ed., Philadelphia, W. B. Saunders Company, 1922, 231 pp.
39. Mackenzie, J. J.: Endocrinology and Metabolism, Loc. cit, 1922, 2, 257.
40. Marchand, F.: Beiträge zur Kenntnis der normalen und pathologischen Anatomie der Glandula carotica und der Nebennieren, Festschr. f. R. Virchow, 1891, 1, 537.
41. Marrassini, A.: Sopra le modificazioni che si hanno nelle surrenali in rapporto con alcune variazioni della funzione e della funzione renale, Lo Sperimentale, 1906, 40, 197.
42. Marshall, E. K., and Davis, D. M.: Influence of Adrenals on the Kidneys, Jour. Pharm. and Exp. Therap., 1916, 8, 525.
43. Moehlig, R. C.: Ductless Gland-cell Control, monograph, published privately, January, 1918, 70 pp.
44. Morgagni: Epistolæ Anatomicæ, 20 a. Cited in Endocrinology and Metabolism, Loc. cit, 1922, 2, 259.
45. Mulon, P.: Notes cytologiques sur le corps jaune de grossesse chez le femme, C. R. Assn. Anat. Suppl., 1909, p. 150.
46. Panella, A.: Action du principe actif surrénal sur la fatigue musculaire, Arch. ital. d. biol., 1908, 48, 430.
47. Podvissotsky (quoted by Vincent, S.): Loc. cit, p. 244.
48. Quinby, W. C.: A Case of Pseudohermaphroditism, with Remarks on Abnormal Function of the Endocrine Glands, Bull. Johns Hopkins Hosp., 1916, 27, 50.
49. Serdioukov, M.: The Functional Relationship Between the Glandular Portion of the Ovary and the Adrenal Cortex, Abstract, Presse méd., 1922, 30, 130.
50. Stilling, H.: Ueber die kompensatorische Hypertrophie der Nebennieren, Virchow's Arch. f. path. Anat., 1889, 118, 569.
51. Strauch, A.: Sexual Precocity in the Male, Am. Jour. Dis. Child., 1918, 15, 132.
52. Stoerk, O., and von Haberer, H.: Beiträge zur Morphologie des Nebennierenmarkes, Arch. f. mikr. Anat., 1908, 72, 481.
53. van Herwerden, M. A.: The Influence of the Adrenal Cortex on the Growth and Reproduction of Lower Organisms, Proc. Konink. Akad. V. Wet., 1922, 33, 1339; Abstract, Endocrinol., 1923, 7, 323.
54. Vincent, S.: Internal Secretion and the Ductless Glands, 2d ed., New York, Longmans, Green & Co., 2d. ed. 1922, p. 93.
55. Wheeler, T. D., and Vincent, S.: The Question of the Relative Importance to Life of Cortex and Medulla of the Adrenal Bodies, Trans. Roy. Soc. Canada, 1917, 11, 125.
56. Zander, R.: Ueber funktionelle und kinetische Beziehungen der Nebennieren zu anderen Organen, speziell zum Grosshirn, Beiträge zur path. Anat. u. Physiol., 1890, 7, 489.
57. Ziegler, E.: A Text-book of Pathology, 11th ed. (English), New York, William Wood & Co., 1908, p. 513.

EPIDEMIC DIAPHRAGMATIC PLEURODYNIA OR "DEVIL'S GRIP."

BY ROBERT G. TORREY, M.D.,

PHILADELPHIA.

(From the Medical Wards and Laboratory of the Philadelphia General Hospital.)

In the *American Journal of the Medical Sciences*, November, 1888, William C. Dabney, published a report entitled "Account of an Epidemic Resembling Dengue which occurred in and around

Charlottesville and the University of Virginia in June, 1888." An excellent description of the clinical features of the disease is given. The characteristics of the disease in the reported epidemics of 1923 correspond closely with Dabney's description. Dabney differentiated the disease from malaria and dengue. He considered it epidemic but not contagious and states that he and a number of his colleagues who had abundant opportunity for observing this condition agreed that it was a disease with which they had not previously met and which had not been described. He states that on account of the agonizing pain on attempting to move or to draw a deep breath a patient had described the condition as "the devil's grip" and it was commonly called by this name in Rappahannock County.

During the summer of 1923 an epidemic occurrence of an acute febrile condition, characterized by severe pain in the epigastrium or chest, was reported to the State Board of Health of Virginia by Dr. Maude M. Kelly as observed by her in two counties in that State. A prompt investigation was made and a report was published¹ by Payne and Armstrong. The condition was designated by them as an epidemic transient diaphragmatic spasm, a disease of unknown etiology, epidemic in Virginia. Hanger, Jr., McCoy and Frantz,² published an article, An Epidemic of Mild Fever of Unknown Nature giving a report of 16 patients admitted to the Presbyterian Hospital in New York after June 6 of that year. They regarded this series of cases as representative of a fairly widespread epidemic, and commented on the discussion in the daily papers of a peculiar malady called "devil's grip" which was said to be prevalent in the New Jersey summer resorts at that time, and in which the symptoms and general characteristics were similar to those found in their cases. These writers designated the condition "epidemic pleurodynia" and considered that the syndrome constituted a clinical entity characterized by sudden onset, pain in the chest or epigastrium, fever of brief duration and a tendency to recrudescence on the third day.

During the latter part of the summer of 1923, the daily papers in the Middle Atlantic States referred frequently to the prevalence of "devil's grip" particularly in Virginia and in New Jersey and it must be concluded that this disease was widely prevalent at that time. The writer's attention was drawn to the condition by conversation with Dr. Charles H. Weber and Dr. William Drayton of Philadelphia in July of this year at which time this disease seemed to be prevalent in Philadelphia, and during the following month he saw a number of cases. The following cases are illustrative and seem to be typical.

¹ Jour. Am. Med. Assn., September, 1923, 81, 746.

² Ibid., p. 826.

Case Reports. CASE I.—Miss M., aged twenty-six years, a nurse, was admitted to the Philadelphia General Hospital Infirmary July 27, 1924, complaining of severe pain in the back. She was apparently well until previous morning though she had been tired at night for a week. She thought that she had strained herself lifting a heavy patient. At 6 P.M., she had a temperature of 101° F., chill at 6.45 and great difficulty in breathing on account of pain with each breath, together with headache and general discomfort. The following morning was breathing easier but headache was very severe. No apparent gastrointestinal symptoms; pain in the lower chest anteriorly and posteriorly and tenderness along lower ribs is very marked.

Examination. Patient is very drowsy; pupils react; tenderness extreme below scapulæ on both sides, breathing causes pain; breath sounds normal, no rales or friction; heart normal size and position, rate 100 regular; abdomen shows slight general tenderness to deep pressure, no localized mass or tenderness; skin normal except for flush of cheeks.

July 28, 1924. During the day the temperature dropped to 100° F., pulse 100, respiratory 30. At 11 P.M., temperature 104° F., pulse 140, respirations 34, blood-pressure 124 to 70.

July 29, 1924. Patient generally feels much better, and is able to breathe without pain. Expansion good and equal, chest resonant, an occasional whistling rale, no friction sounds. There is frequency and irritation on urination.

In the afternoon the pain returned and at 4.30 A.M. the following morning had a chill and rise of temperature to 104° F. Dyspnea and pain became extreme and tenderness over the lower ribs was marked.

July 31, 1924. Much better today. Headache which has been very troublesome has disappeared. Knee-jerks which were absent yesterday are now present but very sluggish. No abdomen reflex or Achilles-jerk. Left pupil larger than right, both react. Pain still present about diaphragm on right and tenderness in back as before. There are no signs of lung involvement and no signs of intra-abdominal trouble. Temperature declined to 98° F., pulse 80, respiratory 24. Drenching sweat.

August 1, 1924. Not as well as yesterday. Epigastric and chest pain and tenderness. Pupils dilated, left more than right. Knee-jerks not obtained. At 2:30 P.M. a slight chill, temperature 102° F., pulse 100. On August 4 there was an exacerbation of pain and tenderness with no febrile reaction. There was marked sweating at night. The patient felt weak and faint and fell to the floor when attempting to walk. She was discharged August 11 and after ten days at home returned to duty. On September 4 she was seen and stated that she felt as well as usual. There was slight tenderness over the lower ribs on the left. No pain on moving or breathing.

The knee-jerks and Achilles tendon reflexes were active. While in the hospital, the erythrocytes numbered 5,030,000; leukocytes 8850 to 11,000. The percentage of the latter was: Polymorphonuclears 62, lymphocytes 28, transitionals 4, basophiles 2, eosinophiles 2. A careful search revealed no plasmodia or stipple cells.

CASE II.—Miss P., a young woman, a nurse, was admitted to infirmary at the Philadelphia General Hospital August 1, 1924, complaining of pain in the chest. She felt well until this morning when she had a chill of short duration about 7:30 A.M. and since then has had slight coryza and felt generally uncomfortable. No headache and no sore throat; no cough or expectoration, no gastrointestinal symptoms. Examination shows pharynx markedly infected and several blebs present. Chest and abdomen are normal, reflexes normal. (Pupil, knee-jerks and biceps). Temperature reached 103° F., pulse 130, respirations 40. Respirations very short and labored; patient irrational at times. Culture of pharynx was reported positive for Klebs-Löffler bacillus. Subsequent cultures negative.

August 2, 1924. Better, temperature 99° F., pulse 100, respirations 24.

August 3, 1924. In the afternoon pain in the chest became acute with feeling of weakness. Knee-jerks very sluggish and difficult to obtain. Temperature 103° F.

August 4, 1924. Drenching sweat—temperature normal.

August 5, 1924. Severe headache and dizziness. Temperature 100° F.

August 6, 1924. Headache. Temperature 101° F.

August 8. Pain in chest. Temperature normal.

Discharged in good condition August 13.

Erythrocytes 4,090,000, leukocytes 11,800, polymorphonuclears 60; lymphocytes 34; transitionals 5; eosinophiles 1. Examination of the red cells by Dr. Small showed an organism described by him in another report (p. 570 this number).

CASE III.—C. C., this patient, on the service of Dr. John M. Cruice at St. Joseph's Hospital was not seen by me but is included because the blood was examined by Dr. Small at the Laboratory of the Philadelphia General Hospital. A chauffeur, white, aged twenty-two years, was admitted to St. Joseph's Hospital, August 71, complaining of pain in the abdomen and at the costal margins on both sides. The family history was negative. Previous medical history was negative. There was no friction sound found, but there was pain and tenderness in the right hypochondrium. Pain in breathing, no mention of cough. The temperature on admission was 103° F. This promptly dropped. There were three slight recurrences of pain with very slight temperature and pulse elevation. The last recurrence was on the 22d. He was discharged August 24 in apparently good condition.

CASE IV.—A man aged twenty-eight years, salesman, had a sudden onset of fever with a chill August 24. He had an agonizing pain in the lower chest with each attempt to draw breath. Temperature was reported as 103° F. There was no cough. The next day he felt better but the following day was again worse. On the afternoon of the twenty-seventh he felt very well and went to work on the twenty-eighth feeling as usual except for slight pain in the lower chest when walking. By noon pain was exceedingly severe on breathing and the temperature had reached 103° F. Headache was severe and sweating profuse. He stayed in bed for a day following this and after that was apparently well.

In the household of this man, a child of seven years was suddenly seized with severe frontal headache and the temperature was found to be 104° F. There was no abdominal pain or tenderness. Vomiting followed an attempt to give a purgative dose. There was a remission in the temperature and another rise to the former level with increase in the headache. The total duration of the attack was forty-eight hours.

Two days later a sister of this child, aged five, had fever and frontal headache with a similar remission and a like duration of the disease. There was no history of dietary indiscretion and no abdominal pain in these cases. Chest pain and pain on breathing was not complained of. These cases do not appear to be typical of this condition as described, but appearing in the same household and following the other case in onset it seems probable that they were manifestations of the same infection.

Discussion. These cases are characteristic of this condition as described by Dabney and the later writers. During the past few weeks I have seen other cases and heard of many cases occurring in Philadelphia. In discussing this condition with many physicians during August, I have been surprised to find that a number of them had just seen patients with symptoms corresponding to this disease. In the latter part of August I was in the central part of Pennsylvania, at a summer resort, and in response to inquiry there, found that there was an epidemic disease prevalent among the native population, not the summer visitors, which from the description of the symptoms, appeared to be the "devil's grip." About 20 typical cases were seen there by Dr. Norman J. Taylor, of Philadelphia.

It is interesting to note that there have been three complete descriptions of epidemics published, two of them within the past year. Hanger, McCoy and Frantz emphasized their belief that this disease was prevalent to the degree when it must be considered epidemic in and about New York City only a year ago, the daily papers in the metropolitan section gave much space last year to the prevalence of this condition, but it still is not generally recognized. The physician should be on the lookout for these cases. They carry a fairly definite symptomatology but may be confused with pleuritis, pneumonia or acute intra-abdominal inflammatory conditions.

Clinical Course. The descriptions of the course and symptoms as given heretofore agree fairly closely. Typically the onset is sudden, often with distinct chill, the temperature is elevated, reaching from 102° to 104° F., and the pulse may be very rapid. It is slow in periods of comfort and is probably increased in rate by the effort to breathe. The pulse curve usually follows the temperature curve proportionately. Pain is the main symptom, occurring in the epigastrium or back or both, and in the lower chest. It is aggravated by breathing or by motion. It is increased during the febrile attacks and decreased as the temperature drops. It is so severe at times as to make breathing almost impossible. With this pain there is very marked tenderness. The tenderness may persist after the pain has disappeared.

Fever and pain come on together, and they diminish together. There may be only one attack, but usually there are recrudescences of pain and fever occurring between twenty-four and forty-eight hours apart.

Headache seems a usual symptom, coming on later than the chest pain. It is usually frontal, it may be severe and persistent. Profuse sweating is characteristic. It occurs late, independent of any rise in temperature.

Prostration is not marked as in influenza. While the temperature is elevated these patients look extremely ill and the pain is severe enough to cause some shock, but as soon as the temperature drops and the pain subsides, they feel surprisingly well.

There is an absence of signs of lung involvement and pleural frictions have not been heard. The knee-jerks may be diminished or lost during the acute stage of the disease but promptly return to normal.

The prognosis is good. Deaths are not reported. Tenderness may persist for some time and the severe cases may feel weak for a long time after the attack. As a rule recovery is prompt and apparently complete. It may be that the disease may show different manifestations in young children. The leukocyte and red cell counts and the urine analysis show nothing characteristic and blood cultures have been uniformly negative. Smears of the blood from 2 of the cases mentioned above were examined by Dr. Small and are the subject of a separate report by him (next page).

There have been no fatalities reported and of course no autopsies in cases of devil's grip. This condition is certainly due to an acute infection, and the recurrences seem like those of a protozoan infection. The pain is probably due to involvement of the diaphragm or diaphragmatic pleura. Tenderness persists in the region of diaphragmatic attachments. We have not studied the diaphragm movements during the acute pain but in fluoroscopic study of our Case I the diaphragm movements were normal and equal on the two sides five days after the last chill.

Quinin was used in treatment on account of points of similarity between this condition and malaria.

The term "epidemic diaphragmatic pleurodynia" seems to designate this condition satisfactorily. It is questionable whether there is an active inflammation of the diaphragm as the change from pain to comfort is so rapid. The severe headache and reflex disturbances noted indicate some degree of nerve tissue involvement by the toxin. The selective localization of the toxic action is very constant. The pain seems pleural, the localization is certainly about the diaphragm.

Summary. A disease with a definite symptomatology which was reported as epidemic in Virginia, New York and along the New Jersey coast last summer has been prevalent in Pennsylvania this summer. Areas of infection have spread. This disease is not as generally recognized as it should be.

The infecting agent has not heretofore been recognized. The disease seems to occur only during the summer months but as yet no insect has been demonstrated to be a carrier. The mode of transmission of infection has not been found.

A study of the red cells for a possible protozoan infecting agent has been made in the Laboratory of the Philadelphia General Hospital by Dr. James C. Small and the results of his study are the subject of the next report in this issue.

A PROTOZOAN ORGANISM WITHIN THE ERYTHROCYTES OF PATIENTS SUFFERING FROM EPIDEMIC PLEURODYNIA ("DEVIL'S GRIP").

(PRELIMINARY NOTE.)

BY JAMES C. SMALL, M.D.,
PHILADELPHIA.

(From the Bacteriological Laboratory, Philadelphia General Hospital.)

THE recent occurrence of epidemic pleurodynia ("devil's grip")¹ in Philadelphia² has furnished the opportunity for making a careful search for the etiological agent of this disease. In considering the clinical manifestations of the disease certain outstanding features have directed attention to the probability of its being caused by a protozoan organism, rather than by a bacterium. Among these may be mentioned: (a) An absence of leukocytosis during the height of the fever; (b) sudden decline of fever with cyclic recurrences, and the relative freedom from symptoms during the intervals; (c) the absence of inflammatory foci, (*e. g.*, upper respiratory or intestinal), which might account for the general symptoms; and (d) an increase of eosinophiles, most marked during convalescence.

Accordingly attention was directed to a study of blood smears. Specimens from two patients were available. The one a nurse (Miss P.) in the Philadelphia General Hospital, diagnosed clinically by Dr. Robert G. Torrey; the other a young man (C. C.) from the medical service of Dr. John M. Cruice at St. Joseph's Hospital. In the former patient 5 specimen smear preparations were made at intervals, during two days; in the other case they were made once only, five days after the onset, but at the time of a mild recurrence of the painful respirations. These preparations were stained with Wright's stain. The Sørensen phosphate solution mixture buffered at pH 6.6 was used instead of distilled water for diluting the alcoholic solution of the stain on the slide.

Specimens from each of the patients showed inclusions within the erythrocytes, which in their more mature forms are illustrated by the photomicrographs. Study of these has led us to believe that they are protozoa. This finding is presented at this time, with a full understanding of the incompleteness of the observations to date, for the purpose of bringing it to the attention of the medical profession in order that others who may have the opportunity might undertake painstaking search for these organisms.

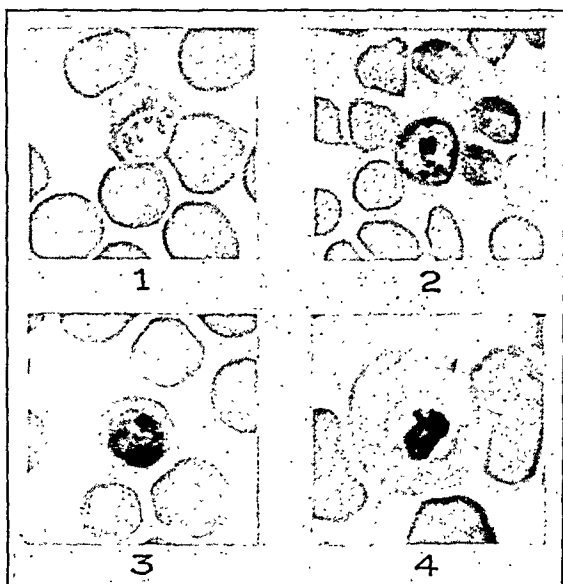
Since the finding of these forms within the erythrocytes of patients suffering from "devil's grip," we have studied preparations of the blood of normal individuals stained with the same solutions and by the same technic. Prolonged search has failed to reveal any inclusions, or any artefacts, which in any way bear a confusing resemblance to the forms mentioned.

The description of these organisms may be presented best by stating the findings in the serial smears of blood from the first patient (Miss P.)

Preparation No. 1, 11.30 A.M., August 5 (Miss P.). The great majority of the erythrocytes appeared normal. A few erythrocytes showing pronounced basic stippling were found. Within certain erythrocytes there appeared small round or oval bodies, usually located eccentrically. They stained a brilliant blue throughout, sometimes with a single red chromatin granule. Little internal detail could be distinguished. The smallest appeared about half the size of a blood platelet. They were easily differentiated from blood platelets, even when the latter appeared superimposed upon an erythrocyte, by their brilliant blue staining as contrasted with the violet staining of the latter. Save for the presence of the inclusion the erythrocyte appeared normal.

Preparation No. 2, 4.00 P.M., August 5 (Miss P.). Here again an occasional stippled cell appeared among the great mass of normal erythrocytes. The round or oval bodies appeared larger, occupying roughly from a fifth to a third of the enclosing erythrocyte. These erythrocytes did not appear swollen, nor did the remaining body appear differently from that of normal adjacent erythrocytes. The

staining again was a brilliant blue. Throughout there appeared threads of dark-staining material which with proper lighting showed a red tinge. These were arranged in a loose skein-like formation or without order.



Plasmodium pleurodyniae within erythrocytes; Wright's stain.

FIG. 1.—Miss P.; 9:30 A.M., August 6, 1924. $\times 1200$.

FIG. 2.—Miss P.; 12:45 P.M., August 6, 1924. $\times 800$.

FIG. 3.—Miss P.; 7:20 P.M., August 5, 1924. $\times 1200$.

FIG. 4.—C. C.; August 22, 1924. $\times 1600$.*

Preparation No. 3, 7.20 P.M., August 5 (Miss P.) (photomicrograph No. 3). Stippled cells were not found. The only abnormal erythrocytes appearing in this preparation were those containing the organisms, which now appear larger in size, so that they occupy the larger portion of the enclosing erythrocyte. There now appears a more definite arrangement of the inner blue mass and the differentiation of a narrow, clear, faintly blue tinged outer zone. Toward one side appears an irregular compact mass of the deeply staining material and several scattered small rod-like particles of the same material. The erythrocyte may or may not appear swollen. In either case a narrow outer zone of the erythrocyte alone remains, which may appear normal, or may be basophilic. Nothing resembling Schüffner's dots has been observed, neither at this stage, nor in the later preparations.

Preparation No. 4, 9.30 A.M., August 6 (Miss P.), Fig 1. In these preparations only the erythrocytes containing the organisms appear abnormal. The organism occupies a large portion of the erythrocyte and maintains a round or slightly oval outline. It is less rich

* Photographs of these preparations showing greater detail and of other phases will be furnished by the author on request.

in the material staining deep blue and this material appears arranged in small round dotlike bodies, which lie scattered irregularly within a pale blue transparent body of the inclusion. This type is shown in photomicrograph No. 1.

Preparation No. 5, 12.45 P.M., August 6 (Miss P.) (Fig. 2). The organisms found in this preparation presented practically the same characters as those found in preparation No. 4. Photomicrograph No. 2 shows one of these in which the large part of the inclusion is made up of the transparent, faintly blue tinged substance with a compact mass of the dark staining material and several scattered particles of the same. It will be noted in the particular one shown in photomicrograph No. 2 that the erythrocyte is considerably swollen. The narrow zone of the red cell surrounding the large organism shows basophilic staining. An erythrocyte "shadow" appears nearby, which probably represents the distorted remains of a cell, in which a parasite had reached maturity. In this preparation similar "shadows" were found with some degree of frequency.

A parasite from the St. Joseph's Hospital patient (C. C.) is shown in photomicrograph No. 4. Others found in the same smear appeared in different stages of development. The striking feature in this instance was the finding with considerable frequency of erythrocytes containing large clear rounded spaces which appeared as vacuoles. These corresponded in size and general contour to the spaces occupied by the larger organisms described above, and did not resemble anything previously seen in stained smears other than in this disease. Distorted erythrocyte "shadows" were also found. It is probable that both of these findings represent erythrocytes from which mature parasites had escaped.

Summary. It is believed that in one patient (Miss P.), where a series of examinations were made, different stages in the cycle of development of a parasite have been observed. The evidence is incomplete, but a striking resemblance to the developmental cycle of the malaria parasite is suggested by our study. The organism is protozoan, but differs from the malaria group in staining characters, in its morphology and in its lack of a destructive action on the contiguous portion of the erythrocyte enclosing it, since where only narrow peripheral zones of the erythrocyte remain, they may yet appear normal in their staining reactions. Pigment granules have not been observed.

In view of these findings the organism is believed to be a heretofore undescribed plasmodium and it is suggested that it be designated *Plasmodium pleurodyniae*.

REFERENCES.

1. Dabney, Wm. C.: AM. JOUR., MED. SCI., 1888, 96, 488.
Payne, G. C., and Armstrong, Charles: Jour. Am. Med. Assn., 1923, 81, 746.
Hanger, F. M., McCoy, C. C., and Frantz, A.M.: Jour. Am. Med. Assn., 1923, 81, 826.
2. Torrey, Robert G.: AM. JOUR. MED. SCI., This issue, 1924, 168, 564.

THE SURGERY OF PULMONARY TUBERCULOSIS.

BY JOHN ALEXANDER, M.A., B.S., M.D.,

ANN ARBOR, MICHIGAN.

(Continued from July, August and September, 1924)

SULTAN extracts an average of 20 to 30 cm.; once he was able to get only 8 to 12 cm. before it broke; once he extracted 41 cm. Not infrequently the stump of the accessory phrenic may be identified on the extracted main trunk, of which it is about one-quarter to one-third the size.

It is known—the original work has recently been painstakingly confirmed by Felix—that the phrenic carries no centrifugal pain impulses. Manipulation of it will, however, sometimes cause the patient severe pain in the chest and in the region of the diaphragm; the chest pain is the result of direct mechanical irritation of the mediastinal pleura by the phrenic nerve, and the diaphragmatic pain results from a cramp-like contraction of that muscle. This pain, or pain in the neck, may be so severe as to require the surgeon to abandon the radical operation. If he has succeeded in extracting as much as 10 cm. of the nerve, it is probable that he has ruptured the accessory phrenic, if present.

There are certain possible dangers of this operation of exæresis: (1) Hemorrhage from the phrenic artery or veins into the phrenic sheath, the blood appearing at the neck. Sultan saw no bleeding in 44 cases; Felix once saw trivial bleeding, easily checked. (2) Hemoptysis, perhaps from an adherent phrenic nerve tugging at infiltrated lung tissue as the twisting proceeds. Zadek saw this twice, but the final results were good; where there is history of hemoptysis he now twists the nerve very slowly. (3) Goetze has seen a cold abscess follow exæresis because the nerve was imbedded in a caseous focus. Sauerbruch would not do this operation in the presence of a tuberculous empyema, or if pleural adhesions were known to exist over the nerve, as the freeing of infectious material might cause a fatal mediastinitis. (4) The twisting may cause reflex cardiac and respiratory disturbances. This occurred in one of H. Alexander's cases, and he was obliged to interrupt the operation. Zadek and Felix have each seen temporary heart and respiratory stoppage. Dyspnea, rapid or slow, weak and irregular pulse are usual during the actual twisting of the nerve. Exæresis has been used extensively in a number of clinics, and no fatal results have been reported, Baer has used it 100 times without mishap; Felix knows of 240 cases (150 of them from Sauerbruch's Clinic) in which it has been performed without accident. It will probably become the operation of choice whenever maximum diaphragmatic paralysis is indicated.

Results of Phrenicotomy Used as an Independent Procedure. Of 60 simple or radical phrenicotomies performed at Sauerbruch's Clinic, 17 showed marked improvement before the supplementary operation was performed. As phrenicotomy produces only partial rest and lung compression, early favorable results often are not lasting; supplementary operations are demanded, as a rule. H. Alexander reports 13 of Sauerbruch's and Schreiber's patients, 12 of whom had bilateral disease and were too sick for a primary thoracoplasty, and 6 of them were too ill for artificial pneumothorax; of these 13, 6 were much improved, 3 slightly improved, 4 not changed. Pribam reported 5 good results: (1) A hemoptysis of three months duration was checked in six weeks and a severe right-sided disease arrested (operation recent); (2) and (3) were huge hemorrhages, and were checked completely; (4) improved enough for thoracoplasty, as were cases (2) and (3); (5) disease of twelve years' duration, very sick and phrenicotomy a last resort, much improved. Sultan reports 12 cases of exæresis used as an independent procedure: 2 patients apparently cured; 5 much improved; 5 unchanged. Fischer did Goetze's radical phrenicotomy upon 17 patients whom he traced from four months to two years later: 7 were cured, 9 much improved and 1 had progress of disease in the better lung. Sauerbruch believes that these must have been only early, and not advanced tuberculous disease. Goetze reports the disappearance of a cavity in midlung after radical phrenicotomy. Frisch and Fischer have used phrenicotomy alone with success in acute disease; Frisch reports a case of "galloping consumption" with fever of 39° to 40° C. and with two cavities in the right upper lobe. After phrenicotomy the temperature became 37.5° C. the sputum was greatly reduced, and with only a few tubercle bacilli. He has seen similar results in other cases. He also reports a case of hemoptysis, apparently being caused by an adhesion between the lung and diaphragm in an otherwise satisfactory pneumothorax, checked by radical phrenicotomy.

Because of the simplicity of the operation and of the excellent immediate results it is certain that radical phrenicotomy will soon be extensively used preliminary to artificial pneumothorax, and thoracoplasty. Because by itself it is rarely able to effect permanent improvement or cure, the temptation should be avoided of using it, because of its simplicity, without intending to supplement it at the proper interval with pneumothorax or thoracoplasty; to do so, and to wait for months in the hope of further improvement, may mean loss of the opportunity to carry out one or the other of these effective measures because of the appearance of active, progressive disease in the better lung.

TUBERCULOUS CAVITY OF THE LUNG. Occasionally tuberculous cavities close spontaneously, but this is exceptional; after compression therapy it is the rule. A great majority of patients who have had thoracoplasty had cavity formation.

Soft-walled cavities are usually easily collapsed by a good pneumothorax or a complete thoracoplasty, but stiff-walled cavities may require one or more supplementary operations, which however, should not be performed for at least six months—until the thoracoplasty has been given every chance to obliterate them.

Paravertebral thoracoplasty should invariably be the first operation performed, and when the cavity is large or multiple or stiff-walled, a parasternal thoracoplasty should be added three weeks later. The two modern supplementary operations are extrapleural pneumolysis, and cavity drainage. The added compression of a firm "fill" after pneumolysis is very often able to cause the cavity wall to "give;" Sauerbruch, who uses a tight gauze tampon, has found that this most frequently occurs on the tenth day. In cases of bilateral cavity, in which the tuberculous disease has become inactive, and where there is a marked shrinking tendency, Sauerbruch and L. Spengler would perform bilateral extrapleural pneumolysis without preliminary thoracoplasty.

When none of the above mentioned operative measures have succeeded in collapsing a cavity, and when its contents are secondarily infected and draining poorly and causing symptoms of sepsis, and when the tuberculous disease is regressing, cavity drainage may be indicated (Sauerbruch, Jessen, Stöcklin, Wagner and Wilms). When these special indications are not strictly observed the results are likely to be very poor.

Sauerbruch was led to advocate drainage by having seen some cases do well after a paraffine "fill" or gauze tampon had ruptured into a cavity and caused spontaneous drainage (before opening the cavity the surgeon must assure himself that the free pleural cavity is walled off by adhesions). At present he sometimes attempts to obtain opening into the cavity in this way, if he fears that it might be difficult to locate it with the cautery; when using this method, sometimes he pares away a part of a greatly thickened pleura, or of a very thick cavity wall (after incision of the lung parenchyma), prior to placing the gauze tampon. Unless the cavity is very near the anterior chest wall, Sauerbruch prefers the posterior route, and never uses the axillary route.

After resection of sufficient lengths of two or three ribs the lung is freed from a few of its pleural adhesions for orientation, and entrance gained to the cavity with a thermocautery (Sauerbruch), or with a knife (Jessen). The retained secretions are scooped out and the cavity "saucerized" and packed with gauze. Jessen would doubly ligate and divide any bands stretching across the cavity. Packing is renewed until the cavity has filled with granulations and become obliterated. A bronchocutaneous fistula usually remains, and frequently may be closed by a musculocutaneous plasty after excision of the mucous membrane in the mouth of the fistula; this plasty should not be performed until at least six months after drainage was instituted.

Sauerbruch reports 18 cases where he followed his advocated sequence, that is, thoracoplasty, pneumolysis and gauze tampon drainage; among them were: 1 early death; 3 deaths after one and a half to three years from progression of tuberculosis in the originally better lung; 8 cures; 6 spontaneous ruptures of cavities, and later healing, although 2 with fistula. One of these patients had had 400 cc of sputum and has now been well for five years. In addition, he reports 8 cases of primary drainage without preliminary thoracoplasty or pneumolysis; of these, 2 died early; 2 improved but retained fistulæ; 4 were much improved, but with fistulæ. Baer reports 3 good results out of 4 large, stiff-walled cavities. Sonnenburg drained 5 patients, and "healed" 3 of them.

The earlier reported results of cavity drainage were very poor; it is only fair to say that no such rigid indications and contraindications were followed then as now. Ten years ago Tuffier and Loewy collected 45 cases; of them 17 died within three months and only 2 were cured. Landerer collected 19 cases: some were temporarily improved, but all died. Landerer "failed" in 3 cases, but none had had preliminary thoracoplasty. Rieckenberg cites a case of honey-combed cavity which was drained through a wound that measured 8 by 4 cm.; the patient could not expectorate well as the force of the cough was expended through the bronchus and drainage wound, and one day he suffocated by drowning in his own secretions. Drainage is contraindicated for multiple and honey-combed tuberculous cavities.

TUBERCULOUS EMPYEMA. Tuberculous empyema is usually secondary to a pulmonary tuberculosis, and often follows the direct rupture of a tuberculous cavity or tubercle into the pleural cavity. Not infrequently it develops from a serous tuberculous effusion that may have arisen during the course of artificial pneumothorax therapy. Empyema secondary to pulmonary tuberculosis is a grave complication and demands rare judgment in treatment.

Effusions may be divided into three main types: (1) Clear serous, with few cells; tubercle bacilli may or may not be found by smear, but are usually found by guinea-pig injection. Onset gradual or sudden, usually moderate fever and absorption in a few weeks; (2) purulent, turbid fluid, with fibrin and many cells and tubercle bacilli, but no pyogenic organisms; stormy onset, high fever, and spontaneous absorption may take place only after many months, or not occur at all; (3) mixed infection with pyogenic organisms; tubercle bacilli may be difficult to recover; diagnosis of tuberculosis may depend upon microscopical examination of a piece of pleura (excised at the time of thoracotomy, which may prove necessary). Tuberculosis may be the underlying infection, even if a pure culture of staphylococcus or pneumococcus is recovered. Mixed infection may occur from a needle puncture (it has been shown experimentally that artificial pneumothorax reduces the resistance of the pleura to infection), or as a metastatic localization of a general

infection, as an influenza, angina, and so forth, or as a result of spontaneous pneumothorax or of rupture of superficial tubercles or cavities during attempts to stretch firm adhesions with high gas pressures in artificial pneumothorax. The mixed infection in this last group is very virulent, and the outcome usually rapidly fatal. When the pleura is much thickened, and the clinical signs of infection are less marked, and the general condition of the patient permits, attempts should be made to kill the pyogenic organisms with antiseptic irrigations by the closed method.

The keynote of treatment is never to institute open drainage of a tuberculous empyema unless it is certain that the secondary infection is uncontrollable by other means. Main reliance is to be placed upon spontaneous absorption or repeated evacuation by aspiration, with or without antiseptic irrigations, and with or without air replacement.

Group (1) effusions (serous) rarely call for any treatment; in case they increase to such dimensions as to cause distressing symptoms from pressure on the mediastinum, heart or stomach, or from encroachment on the opposite lung, partial aspiration would be indicated. To withdraw a little of an effusion sometimes invites spontaneous absorption, but to withdraw all invites prompt recurrence.

Group (2), turbid, purulent effusions without pyogenic organisms, and those cases in group (3) in which the secondary infection does not demand open drainage, call for interference for the reason that these fluids tend to remain and leave chronic, infected empyema cavities, and that deposits of fibrin and organization of the sedimented debris tend to draw a lung, well compressed by artificial pneumothorax, out to the chest wall, and to check the gains that the compression may be making. Repeated partial aspirations may be carried out at whatever intervals the rate of reaccumulation may demand, and it is an almost invariable rule partially to replace the aspirated pus with air or nitrogen gas. Some of the effusion is always to be left in the chest because of its frequently favorable "sero-biologic" effect upon the tuberculous disease. Attempts to kill the pneumococcus and staphylococcus may be made with antiseptic irrigations of 1 to 5000 neutral acriflavine, or 5 cc of a mixture of iodine 1 gm., potassium iodide 2 gm., distilled water 40 cc, in 1000 cc water. Successes have been reported following aspiration of pus, and instillations of 1 to 3000 solution of gentian violet, or 1 to 1000 solution of acriflavin, or 5 per cent methylene blue, or Pregl's iodine solution (Stahl and Bahn), or 1 per cent formalin-glycerin solution (Kahn). Amounts of solution that will not cause marked rise of intrapleural pressure are allowed to flow by gravity through a needle, and then to escape, and this repeated until the recovered fluid is fairly clear, or two needles may be used and the fluid run in the upper one and allowed to escape from the lower one. It is very important that the gas pressure remaining in the pleural

cavity after aspiration be neither too high nor too low; manometer readings during the operation through a needle and tube that are free of fluid are necessary for satisfactory work. To attempt to regulate the gas pressure that is to remain after operation by the subjective symptoms of the patient and cough, is unsafe where a carefully graded lung compression is demanded on account of active pulmonary disease; too high a pressure encroaches upon the opposite lung and causes it to perform dangerous extra work; too little pressure allows the compressed lung to expand and may cause pain and undue dyspnea. At the end of the operation a slightly negative pressure should be left in order to allow for the possible rapid reaccumulation of the fluid. Appearance of a thoracic wall sinus at the site of needle puncture is not an unusual occurrence in these purulent tuberculous empyemata; it should be guarded against by using a narrow-gauge needle for all punctures and by injecting into it a few drops of iodoform-glycerin, or tincture of iodine, as it is withdrawn.

Extrapleural thoracoplasty is indicated for these cases, especially if complicated by bronchopleural or pleurocutaneous fistula, when repeated aspirations fail to obliterate the empyema cavity within a few months, else there is danger that secondary infection may occur (Hedblom), or that the patient may become so weak that an extrapleural or Schede thoracoplasty could not safely be undertaken (Levy). A day or two before operation most of the fluid is aspirated and air substituted, and the patient immediately examined with roentgen-rays to determine the extent of the cavity. The thoracoplasty is then performed in two or three stages, at intervals of two to three weeks, reaccumulated fluid being withdrawn one to two days before each operation. If fluid persists after the completed operation it should be aspirated or it may finally be necessary to perform open drainage and irrigations, and if this does not succeed in obliterating the remains of the cavity a small Schede operation (with primary skin closure—Hedblom) may be required. The Delorme-Fowler decortication operation should never be used on a tuberculous lung. The order of procedure just described is preferable to primary open drainage of the empyema cavity and secondary operations to obliterate it, as there is much less danger of infection of the thoracoplasty wounds. However, if the nature of the case demands immediate primary drainage, and if thoracoplasty is subsequently required to obliterate the cavity, every effort should be made to render the cavity and draining sinus as sterile as possible before making the large incisions for thoracoplasty. This sterilization (tubercle bacilli are not killed) is best accomplished with surgical solution of chlorinated soda (Carrel-Dakin), if bronchial fistulæ do not prevent its use, or if there are no superficial tuberculous lesions of the lung under a thin pleura; these are liable to break down under its disintegrating action.

Acute, virulent empyemata demand immediate thoracotomy,

and this is especially true after cavity rupture during pneumothorax therapy. Sauerbruch resects sections of two or three ribs and tampons the empyema cavity; but even then most of the patients die very soon. Less virulent infections that cannot be controlled by aspiration and irrigation, also demand drainage. Unfortunately any drainage stops the positive intrapleural pressure that may be indicated for the underlying pulmonary tuberculosis, which may progress rapidly, and a draining sinus may remain until death. In the hope that prolonged drainage may not be necessary, and that permanent sinus may not follow, closed, air-tight suction drainage should be tried at first if the pulmonary lesions are such as not to threaten rapid progress following expansion of the lung. Matson *et al.* report 2 complete recoveries by this method, and 3 deaths. Open drainage after resection of a few centimeters of one rib may be demanded, as for any empyema.

It is probable that a large majority of all tuberculous empyemas are complicated by bronchial fistulæ, which are largely responsible for the persistence of the empyemas. When they are small and the intrapleural fluid is not large in amount, they tend to close spontaneously and permanently; when the fluid accumulates in large amounts they may open at intervals to discharge it via the bronchial tree and mouth, and this is dangerous because of the possibility of suffocation, or aspiration tuberculosis, or pneumonia. When the fistulæ are large and do not close spontaneously, they maintain infection of the empyema and repeated aspirations and antiseptic irrigations are rarely successful; however they may be tried, and the patient so placed in bed as to favor plugging of the fistula by fibrin and cellular debris sedimented out of the fluid. Hager attempted to close them by cauterization under thoracoscopic vision. Bernou closed bronchial fistulæ in 2 cases with massive intrapleural injections of "huile gomenolée." Most cases of large bronchial fistulæ with persistent empyema fluid require eventual extrapleural or Schede thoracoplasty, which is often successful in closing them.

Results. Hedblom has recently reported a series of 74 tuberculous empyemata, all operated upon; 16 were cured, 11 in good health with sinus, 12 improved, 3 not improved, 10 operative deaths, 15 later deaths, 7 results unknown. Sauerbruch's statistics are given on page 413. In addition to their 5 cases mentioned just above, Matson *et al.* report 5 others operated elsewhere by open drainage; 3 of these died, and 2 required secondary thoracoplasty.

POSTOPERATIVE COURSE, COMPLICATIONS AND MANAGEMENT. Some surgical shock is to be expected after thoracoplasty, but it is surprising how well sick tuberculous persons withstand the major operation.

For the first few days there are pain, increased fever and pulse and difficult expectoration, and perhaps cyanosis and dyspnea. At this period, when the system is being flooded with large amounts

of toxins which have been squeezed out of the compressed lung, and a so-called negative phase exists, when general resistance is low, all tuberculous lesions are susceptible to a "flare-up." Usually within one to three weeks the symptoms of toxicity disappear, the expectoration, temperature and pulse decrease, and the appetite, weight, general appearance and mental disposition greatly improve.

There is usually considerable pain in the chest, shoulder and arm for the first days after operation, especially after the removal of the upper ribs, when the brachial plexus may be dragged upon. Sometimes the patient splints the chest by holding the arm snugly against the operated side. Persistence with active movements of the arm during the first month, as after breast amputation, almost invariably succeeds in ridding it of its stiffness and in restoration of practically perfect function. It occasionally happens that some of the intercostal nerves become entangled in scar tissue or regenerating ribs,

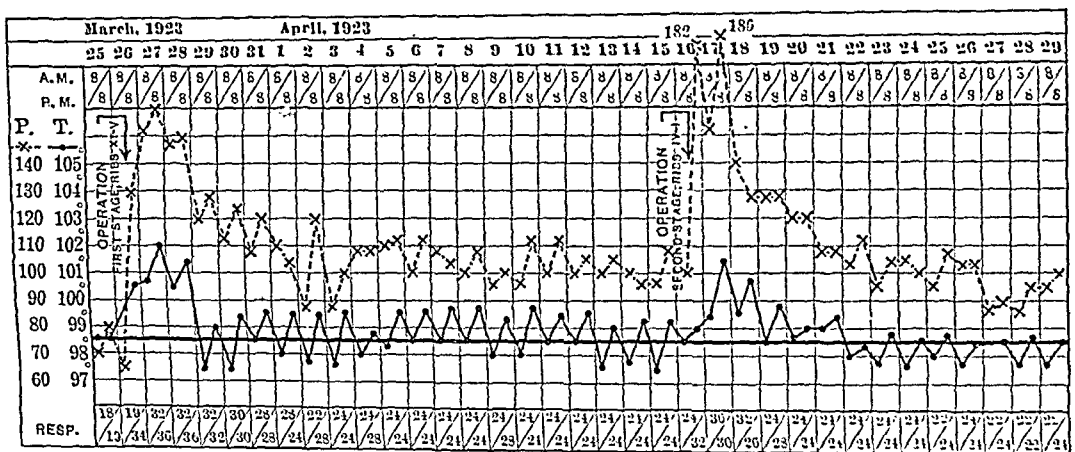


FIG. 12.—A. H., a typical postoperative chart of a satisfactory two-stage para-vertebral thoracoplasty. See Figs. 3, 4, 5 and 13 for photographs of this patient.

or become caught between rib stumps, and severe intercostal neuralgia may be the result. Such cases may later need resection of the affected nerves. The posterior rib stumps may be tender to pressure, if they have been left unduly long. "Snapping scapula" may attract the patient's attention; it is due to the slipping of the vertebral border of the scapula past the posterior rib stumps.

Position in Bed. It is preferable that the patient lie slightly on the side operated upon during the first weeks after operation; this increases lung compression and rest and aids him to expectorate. Sauerbruch, with the aid of rubber rings and pillows, places the patient in the semisitting posture with the foot of the bed slightly raised, and inclines him a little toward the side operated upon by putting a pillow under the other side.

Poisoning from local anesthetic has been discussed under the section "anesthesia."

Because of the operative trauma and of the squeezing of many

toxins into the general circulation, the temperature and pulse mount rapidly after operation; 39° C. and 120 pulse are to be expected. Usually at the end of a week they decline to normal (if the operative indications and compression have been favorable). If temperature and pulse remain very high for more than a week the prognosis is poor; if they fail to drop to nearly a normal level within two to three weeks, pneumonia or a spread of the tuberculous disease is to be feared, and especially if the temperature drops for some days or weeks and then mounts. Bull has reported several cases in which the temperature was 102° to 104° , and the pulse 120 to 140 for two to three days after operation, but then behaved in the usual manner; one patient died the day after operation with a temperature of 106° , and at necropsy nothing could be found to account for death.

Cough and expectoration are made difficult by operation because of pain, lessened thoracic excursion and perhaps paradoxical respiration. In order to avoid retention of secretions and aspiration pneumonia, it is of paramount importance that the patient be enabled to expectorate. Even after lung compression the secretions are easily carried by the ciliæ to the bifurcation of the trachea, from which point they must be raised by coughing. Small, frequent, ineffectual and exhausting coughs must not be permitted. Alleviation of pain is prerequisite to effective coughing; morphin must be *regularly* given in doses sufficient to permit coughing; Sauerbruch gives them for ten to fourteen days, and then stops them altogether. During the first few days after operation it is important that a nurse be in constant attendance at the bedside to support the operated side during every coughing spell; she slips one open hand around to the back of the chest, and places the other anteriorly, and exerts gentle pressure. She urges a deep breath and a good cough. Eloesser advises turning the patient in bed twice a day in order to aid the patient to "drain out" the accumulated secretions. Simple retention of secretions may sometimes be differentiated from true pneumonia by the facts that the sputum is less rather than more in amount, and that there is no undue dyspnea or bad general condition, and that when the secretions are finally expectorated the temperature drops.

During the first few days after operation the amount of sputum is greatly increased, and then it rapidly decreases. The sputum curve, which closely follows the temperature and pulse and weight curves, is of great importance for prognosis. Between the first and second stage operations there is usually first a decrease in sputum amount, and then an increase; however, if the final stage operation is followed by a decrease and then an increase the prognosis is not good. Within a few months of many successful thoracoplasties sputum completely disappears. It is possible that the active tuberculous disease might have been completely checked, but the cavity not entirely obliterated and its walls secrete 5 to 10 cc of sputum, with or without tubercle bacilli. The tremendous improvement in

sputum, temperature, pulse and weight curves, and in the general condition of the patient are frequently so sudden as to seem a miracle. Sputum that was characterized by pus and semisolid lumps before operation becomes shiny, frothy mucus and the tubercle bacilli at first degenerate and then disappear. Disappearance of the bacilli may take several months, but their persistence does not necessarily mean that the prognosis is bad, as it is known that a few small "open" lesions may persist for many years in clinically well persons.

After every thoracoplasty there is some circulatory disturbance (Jessen), and camphor, caffein, digitalis and possibly oxygen inhalations may be indicated. Loosening or tightening of the dressings may be of service. The cardiac displacement is well withstood, and most often is simply the return of the heart and mediastinum from the position to which it had been drawn by the shrinkage of the tuberculous lung to its old normal position. The great intrathoracic vessels are never kinked or stenosed. Guilleminet has reported a partial stenosis of the subclavian vein for several days. Permanent extra load is imposed upon the heart only when the lung and its bloodvessels become greatly narrowed by the compression and new fibrous tissue.

A certain amount of dyspnea may be expected for a week; it may be caused by the toxemia, the pain, or the cardiac disturbances, if they occur, and by the paradoxical respiration and mediastinal encroachment upon the better and functioning lung. A too tight or a too loose wound dressing may be responsible. Morphin usually controls it. A high enema may remove a mass of feces and an accumulation of gas which are restricting the movements of the diaphragm. Even climbing stairs or hills months after operation may not cause dyspnea.

Wound Dressing. After operation the wound should be well protected with gauze and cotton, and firmly compressed; this is best accomplished by broad adhesive straps taking origin from the opposite shoulder and loin regions, but not from the opposite mid-chest, and not encircling the chest, else the function of the uncompressed lung would be interfered with and the patient distressed. Sauerbruch has 10 cm. long elastic cloth sewn in the middle of the adhesive straps in order better to aid the patient when coughing. Jacobaeus and Key make a plaster-of-Paris shield before operation to bridge the less diseased hemithorax; it rests on the hip and shoulder; after operation circular bandages may be wrapped firmly around this without prejudice to the respiration of the better lung. The wound drain used for accumulating serum, should be removed in twenty-four to forty-eight hours. The entire dressing, which soon becomes wet or stiff, and uncomfortable and a breeding place for germs, should be changed in forty-eight hours; Sauerbruch, however, does not change it until the eighth day; Ochsner and H'Doubler have sewn a wound with catgut and left a circular bandage in place for weeks, believing that it is important not to

interrupt pulmonary rest; Davies uses a many-tailed bandage and does not dress the wound for ten to fifteen days. For ease of coughing and for the patient's comfort, and in order to obtain maximum compression, it is advisable that some sort of support be worn for several months, or until the chest has become fixed by new bone formation from the rib periosteum. A convenient form of pad, taking its points of counterpressure from the opposite hip and shoulder, is pictured in Fig. 13. Leonard Freeman prefers a modified hernia truss, which touches at the spine and where the compression is desired, and leaves the uncompressed lung free for normal respiration. Bérard and Dumarest use a padded corset. Jacobaeus and Key lay sand bags on the operated side for awhile each day.

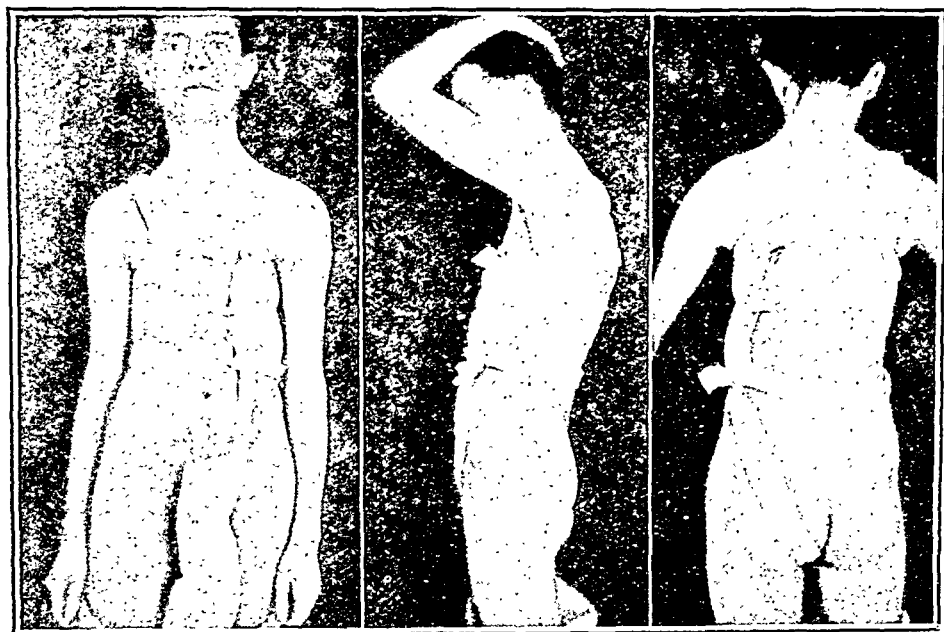


FIG. 13.—Pad and elastic band appliance worn after thoracoplasty to increase pulmonary compression.

Because of the proximity of superficial cavities and a pleura which may be latently infected, wound infection may occur more frequently than after other presumably clean surgical incisions. Burnard has reported the death of a forty-year-old man from septicemic wound infection. Stöcklin reports 8 total wound infections with 3 deaths among his 100 cases. Two of Sauerbruch's 4 cases of postoperative psychosis followed wound infection; both recovered.

Pulmonary Complications. Next to cardiac failure, spread of disease to the uninvolved portions of the compressed lung or, more frequently to the opposite lung, is the most dangerous postoperative complication. The new foci may appear as any type of tuberculous lesion, including tuberculous pneumonia, or as a non-tuberculous lobular or lobar pneumonia. The patient may become dyspneic and cyanotic, and the temperature and pulse mount rapidly; if the

disease is in the uncompressed lung, new coarse rales and the usual changes in the other physical signs may be demonstrable, but if in the compressed lung, the physical signs are so distorted as to be of no diagnostic value. In addition to the usual treatment for pneumonia, oxygen inhalations may be found useful because of the great reduction of breathing surface by the operation and pneumonic infiltration.

Postoperative hemorrhage may occur in the wound and require pressure or ligation, or a hematoma may need repeated aspirations. If there is hemoptysis from within the lung the head of the bed should be lowered and accumulation of blood, and possible aspiration prevented by insistence upon adequate expectoration.

Brauer and L. Spengler saw serous effusion appear on the unoperated side in two patients one and a half and six and a quarter years, respectively, after operation; both were acute and both were aspirated as often as dyspnea demanded, and both disappeared within five weeks.

Although miliary tuberculosis has been known to follow nephrectomy, removal of lymph glands, arthrectomy and lobectomy in tuberculous persons, it has been reported only once after thoracoplasty (Willy Meyer), and in this case a preoperative infection cannot definitely be ruled out.

The so-called "negative phase," which occurs when the system is being over- (auto-) tuberculinized by the squeezing of toxins out of the compressed lung, may be responsible for the activation of latent tuberculosis in the intestines, bones, lymph glands, epididymi or kidneys.

Sauerbruch does not permit his patients out of bed until from two to three weeks after the last operation; those who have had the two-stage operation remain under surgical supervision for about two months. Bérard and Dumarest get their patients out of bed the tenth day, and five days later return them to the sanatorium; they combat scoliosis and limitation of arm function, after the first week, with respiratory gymnastics and passive and active arm movements; their patients wear padded corsets. Stöcklin fears embolus, so he "soon" has his patients sit on a stool to exercise. Brauer also does this "soon," and places a weight on the patient's head, and has him bring one arm after the other to it; this he believes assures a straight spine and good arm function. Hug found from an examination of 22 of Sauerbruch's and Schreiber's cases that those who stayed in bed for at least six months after operation had the least spinal deformity. It is of the utmost importance that all patients who have had thoracoplasty follow a strict hygienic régime, preferably in a sanatorium, for at least six months after operation. As a result of his long experience, Sauerbruch insists that the postoperative "cure" is necessary to clinch the favorable action of pulmonary compression, as it is during the succeeding months that the fibrous encapsulation of the lesions occurs.

Physical Examination of Chest. Compression of a lung changes the physical signs of the whole chest. The uncompressed lung becomes emphysematous, and the heart and both lung outlines are difficult to determine. The heart may give forth whirrs and functional systolic murmurs because of altered conditions of position and pressure. *The compressed lung, even after its disease has become wholly arrested, presents the physical signs of active tuberculosis,* and the roentgen-ray aids but little, except that sometimes it is able to show whether or not cavities are obliterated. Judgment of the clinical condition of the compressed lung must be based wholly upon general symptoms, the temperature, weight, sputum amount, character and tubercle bacillus content, the ability to work, etc., provided, of course, that the other lung and other organs can be excluded as the sources of activity. For years the compressed lung, even in the total absence of catarrh or sputum, may be full of coarse and fine rales and a variety of bizarre noises; breathing is loud and bronchial above, and distant or absent below; the whole lung is dull to percussion, and the upper lung, because of the trachea and large bronchi, is tympanitic; fremitus may be altogether absent. Bronchiectases and cavities remaining open may give resonating rales and a Wintrich's change of note. Gross respiratory movements are minimal, except of the upper anterior chest, these being largely transmitted from the opposite side via the sternum.

The uncompressed lung shows the physical signs of emphysema which may obscure the signs of small active lesions. Attempts must be made to differentiate the rales of active disease from those transmitted from the inactive, compressed lung.

DEFORMITY. After the old Brauer-Friedrich operation deformity and functionable disability were considerable; after the modern paravertebral operation there is rarely any appreciable deformity, certainly none that can be detected through the clothes, and no appreciable loss of arm and shoulder function. Certain anatomical changes do, however, occur, and to a more marked degree in the plastic chests of young people with weak musculature than in stout, middle-aged people whose strong muscles and ligaments make for thoracic stability. Archibald and Brauer report almost no deformity after thoracoplasty, but Hug, after a detailed examination of 22 of Sauerbruch's and Schreiber's operated patients who were found still "curing" at Davos, found some deformity in all of them, and almost all of which, in his opinion, might have been prevented by a sufficiently long postoperative rest in bed (that is, prevention of early weight bearing by the spine), and proper pad and bandage support. Stöcklin orders supporting corsets only in rare cases; Bérard uses them. Deformity does not reach its maximum for one year, unless checked by gross regeneration of bone from the remaining rib periosteum.

Hug, an orthopedist, thinks the likelihood of severe skeletal deformity after thoracoplasty upon patients less than twenty-years old

should create at least a tentative contraindication to the operation. He would attempt to obtain the desired compression with a partial pneumothorax and a pneumolysis, which are non-deforming. On the other hand Brauer and Sauerbruch would expect little deformity after thoracoplasty upon young persons if only short lengths of rib were removed.

The narrowing of the chest occurs chiefly in two directions: (1) A marked diminution in the horizontal diameter. Hug measured 3 patients at the xiphoid level and found the differences between the operated and unoperated sides to be 7, 11, and 13 cm. respectively

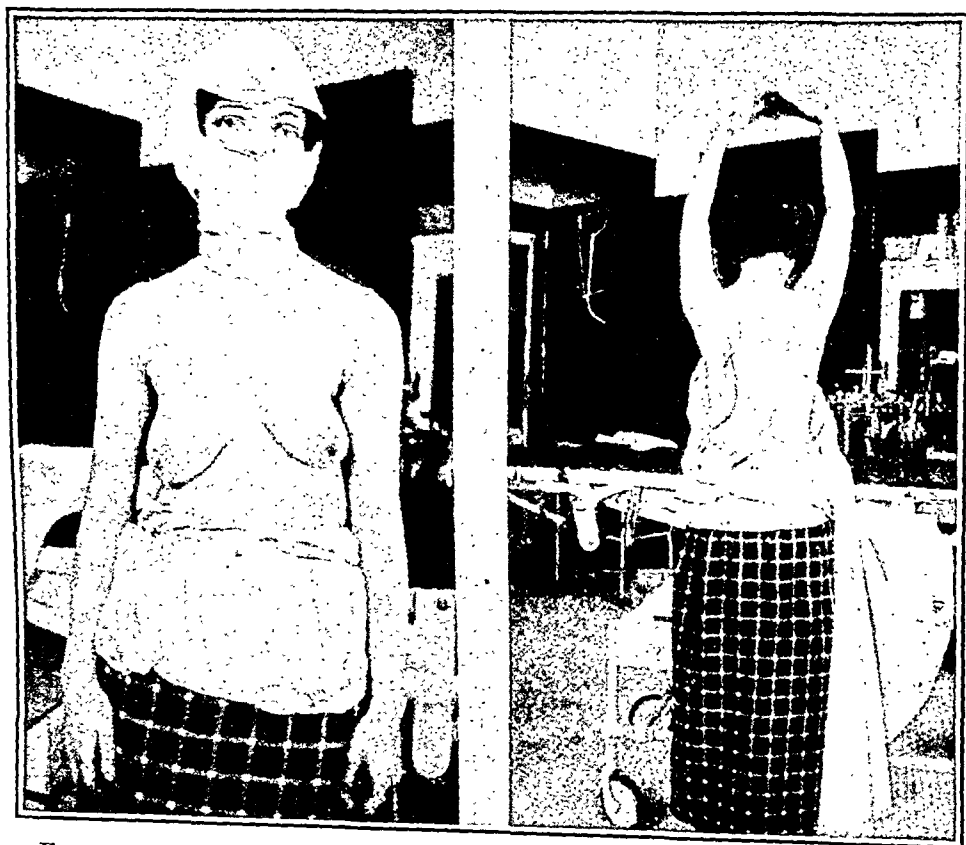


FIG. 14.—M. D., little gross deformity; the scars have been inked for the photograph. No functional disability. Operation one year ago. Now no expectoration nor any other evidence of active tuberculosis.

(see Fig. 2). (2) A sinking or settling of the whole hemithorax for a distance of one or two interspaces; the cut end of the peripheral first rib stump takes its place opposite the central stump of the third rib. The shoulder and axilla usually sink 1 to 5 cm., but may sometimes actually be held higher than normal by the semiconscious efforts of the patient. The vertebral border of the scapula may be caught beneath the vertebral stumps of the ribs. The clavicular fossæ are deepened, and the costal border may bulge or settle toward the iliac crest. If the lower intercostal nerves have been paralyzed the hypochondrium and epigastrium may protrude,

especially on straining and coughing. The chest just below the scapula may be much depressed. The opposite emphysematous lung causes its hemithorax to expand and to shove the lower sternum toward the operated side and to tilt it toward the compressed lung. Because of some cervical kyphosis the head may bend slightly forward, and the face turn toward the operated side; the central ends of the first and second ribs may appear as prominences in the supraclavicular triangle.

Thoracoplasty is usually followed by some scoliosis, but it is rarely of marked degree. Prior to operation the more diseased lung has usually caused a scoliosis concave toward the same side. Thoracoplasty upsets the thoracic balance, detaches muscles and ligaments, and the supporting muscles of the side operated upon atrophy to some extent; as a result the original spinal curve straightens out, and often forms in the opposite direction, that is, convex toward the operated side. The maximum convexity is in the upper two-thirds of the chest. The amount of scoliosis is roughly proportional to the number and length of ribs resected, and to the lengths of the posterior stumps, as well as to the youth of the patient and skill in post-operative management.

After months some compensatory scoliosis, in the opposite direction, appears in the cervical and lumbar spines. Because of the operative traumata to the paravertebral muscles, the scaleni and the diaphragm gain an advantage in strength over the posterior spinal muscles, and slight kyphosis results. Brauer declares that he has never seen these kyphoscoliotic changes described by Hug, but Stöcklin writes that they always occur to a slight extent.

Operative traumata to muscles, ligaments and ribs, and the subsequent scar formation combine to immobilize, or almost to immobilize, the hemithorax, and the thoracic spine becomes almost rigid, movement occurring in the cervical and lumbar regions. This functional impairment of the chest is scarcely known to the patient, subjectively, but it does serve to obtain the much desired pulmonary rest.

RESULTS. Because the prognosis in pulmonary tuberculosis is notoriously uncertain, and because its surgical therapy is in a state of flux and imperfectly standardized, it is not entirely trustworthy to base judgment of surgical treatment upon statistical reports. The majority of patients presenting themselves at one clinic may be well-to-do and able to continue hygienic treatment after operation as long as advised to do so, and may be in the earlier stages of the disease; if they are carefully sifted for operation according to a rigid observance of predetermined indications and contraindications, and if operated upon skilfully and completely, and wisely cared for after operation, the results may well be expected to be excellent—and so they are. If another clinic accepts for operation patients with bilateral tuberculous activity, and performs incomplete and partial operations in the hope that at least a little good may be

accomplished, and does not insist upon adequate postoperative hygienic régime, disappointments are certain and the ultimate clinical results may be expected to be bad. Table II clearly demonstrates the difference between these two types of clinic.

Sauerbruch has reported 134 patients (35 per cent) cured out of his first 381 cases, which were operated upon according to a great variety of methods; there was a mortality of 2 per cent during the first days, and 10 per cent additional within the first four weeks, and 23 per cent additional after the first month, a total mortality of 35 per cent; the remaining 30 per cent included many "improved," some "no change," and a few "worse." Percentage figures for his 339 thoracoplasties, supplemented sometimes with other operations, (and which correspond closely with the figures given by other most experienced surgeons) are: cured and improved 61.6 per cent; worse and early and late deaths, 33.6 per cent; miscellaneous (no change, under treatment, and result unknown), 4.8 per cent. Stöcklin and Schreiber report 62.5 per cent "positive results," and 37.5 per cent "negative results." My collected series of 1024 cases reported during the past six years, shows: cured, 32 per cent; improved, 26 per cent; worse, and early and late deaths, 35 per cent; miscellaneous, 7 per cent. Many interesting facts may be gathered from a careful study of Tables I and II.

Mühsam and Zinn deny the permanency of the early favorable results of thoracoplasty, and say that because it is rarely able to produce sufficient compression, relapse occurs after one or two years. It is true that incomplete operations may cause an initial improvement, but are not enough to render the disease permanently quiescent. There are a considerable number of patients who are now known to have been perfectly well and able to do hard work for six or ten years and more after the complete operation, and these undeniably demonstrate the permanency of thoracoplasty results. Some patients properly operated upon do die after initial improvement, but with rare exceptions these deaths are directly due to progression of the disease in the uncompressed lung, or in other organs than the lung—disease which is beyond the control of the operation, except insofar as it is able to raise the general bodily resistance. Brauer estimates that tuberculosis progresses in the better lung after operation in 10 to 15 per cent of all cases.

The immediate operative mortality of thoracoplasty upon well selected cases is about 2 per cent. If every complication that might be attributed directly to operation is counted, and the time not limited to the first few days after operation, the mortality is from 10 to 15 per cent; 12.3 per cent is the figure for my 1024 collected cases; 10 per cent is Bull's and also Saugmann's figure; Bull reported a mortality of 11.9 per cent among 67 operations during eight years by Norwegian surgeons other than himself. Some years ago Wilms reported 23 cases, operated by himself by his technic, without an operative death.

TABLE I.*—TABULATED RESULTS OF 1024 THORACOPLASTIES REPORTED 1918-1923.

Reporter.	Year reported.	Number of patients.	Apparent complete cure.†	Clinical cure ‡	Considerable improvement.	Improvement.	No change.	Worse.	Under treatment.	Result unknown.	Deaths.	Remarks.
Archibald . . .	1923 and 1924	40	5	..	10	5	1	..	4	1	14 (1, 6 days after 2-stage Brauer-Friedrich operation, 1912; 1 heart failure, 12 days; 1 wound infect., 21 days; 2 following 3d stage op. of ant. apicolysis (pur. bronchitis, 6 days; heart failure, 15 days); 9 after 7 weeks (1 typhoid, 8 tuberculosis))	13 (5 "consid. impr.," 3 "impr.," 4 "under treat.," 1 "result unknown") have been under treatment less than 1 year; rib I resected in all but earliest cases; otherwise typical Sauerbruch resections; 3 had partial thoracoplasty added to partial pneumothorax; 5 had 3d-stage pneumolysis and muscle "fill;" almost all had some tuberculosis in the better lung.
Brauer and Spengler . . .	1923	35	..	13	..	15	..	3	4 (1 tbc. opposite lung, 8 weeks; 1 better lung full of scar tissue (so asphyxia); 1 aspiration food to opposite lung while laughing, 10 days; 1 sputum aspiration to opposite lung, 12 days)	All by Brauer's subscapular, paravertebral op.; this partition of the 35 patients derived from calculation from author's statement that 4 died, 38 per cent "very well influenced or practically healed" and 42 per cent "substantially improved."
Brown and Eloesser . . .	1923	5	..	3	2	Observed 1 to 2 years; all women; all chronic fibroid tbc. with cavity (3, huge); in 3 slight disease by roentgen-ray (rules in 1) in better lung, but no progression occurred.
Bull	1922	75	25	9	..	12	..	29 (8 from operation; 20 from tbc.; 1 from other cause)	64 of the 75 observed 1 to 8 years: 38 alive, 25 clinical cures, 26 dead; 37 observed 3 years and more; 12 clinical cures, 1 has tbc., 3 uncertain, 21 dead (4 of op., 16 of tbc., 1 of flu); the 9 "no change" cases classified by reporter as "alive and tuberculous."

Burnand . . .	1922	7	..	6	1 (septicemia from wound infection)	Roux the surgeon: "Results so satisfactory, so rapidly satisfactory, so complete."
Christensen . .	1919	13	7	6 (of tbc., 2 to 15 months; 0 operative deaths)	6 of the 13 had bilateral disease; 10 operated at one sitting; the 7 "considerable improvement" cases classified by reporter as "more or less working."	
Cordier and Gardère	1923	1	1	Very small resections.	Resects only a few cm. anterior to and 1 to 2 cm. posterior to rib angles; never resects rib I; observed 7 and 18 mos.
Descarpentries .	1923	2	2	2 patients questionably suitable for op.	Cavities and great retraction of hemithorax and traction on heart, which decompensated; all corrected by Wilms operation.
Edwards . . .	1923	3	1	..	1, 3d day of heart failure	
Frisch . . .	1921	1	1	
Gravesen (Saugmann)	1923	105	..	41	2	21	3	38 (9 operative deaths; 29 later of tuberculosis)	Of the 21 "impr.," 2 died later of influ.; some had supplementary parasternal resections and 3 had pneumolysis (1 fat "fill" cured; 2 gauze "fill" (1 gt. impr.; 1 died later)).
Guillemenet . .	1923	27	9	..	5	..	1	4 (3 operative deaths, 3 to 12 days; 1, 3 months after op. (had bronch. fistula))	Op. by Bérard, Santy, Patel, Roux and Leriche; wide resections; of the cures, 3 were partial op.; 2 of those under treatment suffered from tbc. empyema.
Hannema . . .	1918	1	1	Cavity and hemorrhages before ant. and post. Wilm's op.; "saved her life;" observed 15 months.
Hauke . . .	1923	9	..	3	1	..	1	21 (5 operative deaths, 7 days to 1 mo.; 11, later of tbc.; 5 of other causes)	3 to 9 months' observation.
Jacobaeus and Key	1923	44	12	8	3	These patients all operated upon over 1½ years; in 46 some pathology by ph. exam. or roentgen-ray in better lung; in 6 slight hilus thickening; only 8 absolutely negative.
Jacobaeus and Key	1923	16	3	11	2	These patients observed less than 1½ yrs.
Jessen . . .	1921	(20)	"10 favorable and 10 unfavorable results;" these 20 cases are insufficiently classified to be included in table totals.
Johnston . . .	1922	1	1	1st stage, ribs I to V anteriorly; 2d stage, 3 months later, 5 to 10 cm. of ribs XI to V posteriorly.

TABLE I.*—TABULATED RESULTS OF 1024 THORACOPLASTIES REPORTED 1918-1923.—(Continued.)

Reporter.	Year reported.	Number of patients.	Apparent complete cure.†	Clinical cure.‡	Considerable improvement.	Improvement.	No change.	Worse.	Under treatment.	Result unknown.	Deaths.	Remarks.
Lilienthal . . .	1923	12	1	..	1	7	1	2 (within 4 days of op., of acute pulmonary edema)	Sauerbruch technic; always took first rib; in 1 he added pneumolysis and fat graft; in 4, preliminary resection of phrenic nerve; 3 of the 7 "improvement" had tbc. empyema.
Meyer, Willy . .	1923	5	1	1	3 (miliary tbc.; 6 days after 2d stage; 48 hours after 1st stage, probably from novocain poisoning)	All had more than a little active disease in the better lung; first rib not resected except in the "improvement" case (improvement only temporary); this patient had tbc. empyema and cold abscesses and bilateral disease; the cured patient has been well 4 years.
Moreau and Olbrechts . .	1923	1	1	6 (1 aspiration under narcosis; 2, 1 day; 3, 17 days; 4, 2 months of tbc.; 5, improved, but death 3 years later, Potts; 6 improved for 4 years, then died in 6 months of tbc.)	139.5 cm. resected; observed 9 months. All but deaths 2 and 3 presented ideal indications for operation; does not mention technic used; believes poor results due to post-war economic conditions in Germany.
Mühsam . . .	1919	8	1	..	1	3 (tbc. some months after op. 3 (1 op. shock, day of 1st stage, ribs X to V; 1 of tbc., 2 years postop. (had been greatly improved for 1 year); 1 of acute non-tbc. abd. illness after being cured of tbc.)	Quoted by Madinier. Considerably improved patient had only ribs X to VII resected; none of the others had ribs I or XI resected.
Nyström . . .	1919	13	..	9	1	2 (1 operative death, 7 days; 1 after 4 months)	
Ochsner . . .	1923	4	
Ranzi . . .	1922	12	..	5	..	2	..	2	..	1	..	Resected rib I unless clinical findings and roentgen-ray showed apex "relatively free."
Riviere and Romanis . .	1923	2	1	1	Resect relatively short rib lengths.

Sauerbruch	1920	71	28	..	12	31 (2 in first few days after a 1-stage op.; 1, 9 days from aspiration; 28 died later)
Sauerbruch	1920	223	84	..	6	41	18	74 (3 operative deaths; 26 in first 3 weeks, pneumonia, aspiration, mediastinitis, progression tbc. in better lung; 45 after 4 months)
Sauerbruch	1920	26	15	3	2	..	5	1 (pleural infection following operative tear of pleura)
Brunner (Sauerbruch)	1922	116	18	..	27	31	12	28 (13 within 4 weeks: 1 on second day, 12 after second week from heart, pneumonia and wound disturbances; 15 deaths 1 to 12 months, mostly from progression tbc. in better lung)
Sayago and Allende	1921 and 1922	2	1	1
Schottmüller Shivers	1918 1923	1 27	1 3	..	4	2	1	3	1	10 (5 during first week; 2 during first month; 1 during second month; 2 after 2 months (including 1 after 2½ years' improvement); the causes of death: pneumonia, wound infection and influenza)
Shortle and Gekler	1922	4	2	2 (1 from heart failure and dropsy after first stage; 1 from heart failure ninth wk.)
Stöcklin	1922	100	37	..	5	19	1	38 (24 early deaths: 11 heart failure, 3 wound infection, 4 aspiration pneumonia, 2 hemoptysis and aspiration pneumonia, 2 emboli, 1 novocain poisoning, 1 nephritis, 11 deaths of tbc., 3 months to 3 years; 3 deaths from intercurrent disease after improvement for 4 months to 1 year; no deaths in last 18 cases—careful selection)

These by old Bruner-Friedrich op. (9 op. in 1 stage, 38 in 2 stages, 24 in 3 stages).
Sauerbruch paravertebral operation; 84 cures observed 1½ to 6 years.

Partial thoracoplasty (usually ribs I to VII), combined with partial pneumothorax; cures observed 1½ to 5 years.

Reported by Brunner; cases operated since those published in 1920; none of the 27. "considerable improvement" cases had tubercle bacilli at time of report.

"Improvement" case observed only 1 month; 1st rib not removed; "considerable improvement" case had basal disease and cavity, and only ribs X to VII were resected.

Was advanced tbc.; observed 3 years.
1 Schede and 26 Sauerbruch operations; 1st rib resected in 3 cases; pneumolysis attempted in all but 3.

Both deaths occurred in patients who were "terrible risks."

All operated by Schreiber 1913-1920; extensive (110 to 140 cm.) resections of ribs XI to I inclusive, and in addition most had apicectomy without "fills," and "cure" had failed; 30 had partial pneumothorax at time of op.; 25 of the 37 cured patients were observed over 2 years; 3 of the "improvement" cases relapsed after being "cured" 4 to 5 years.

TABLE I.*—TABULATED RESULTS OF 1024 THORACOPLASTIES REPORTED 1918-1923.—(Continued.)

Reporter.	Year reported.	Number of patients.	Apparent complete cure.†	Clinical cure.‡	Considerable improvement.	Improvement.	No change.	Worse.	Under treatment.	Result unknown.	Deaths.	Remarks.
Welles	1923	11	1	.	6	1	3 (2 after 2 weeks from wound sepsis and pneumonia in better lung; 1 after 5 months, of tbc.)	In all but 1 (later required pneumonolysis and "fill"); 3 to 17 cm., ribs XI to I resected; 4 of the "consid. impr." still under sanatorium treatment.
Whittmore and Chaffin . . .	1921	1	.	.	.	1	Resected 2 to 11.5 cm. ribs I to XI, inclusive, and added a small pneumonolysis without "fill."
Total	1024	243 (23.8 per cent)	85 (8.3 per cent)	95 (9.3 per cent)	173 (16.8 per cent)	13 (1.3 per cent)	36 (3.5 per cent)	27 (2.6 per cent)	28 (2.7 per cent)	<div> <div>126 (12.3 per cent) were directly connected with operation</div> <div>198 (19.3 per cent) not directly connected with operation</div> <div>324 (31.6 per cent)</div> </div>	Most of the late deaths were from tuberculosis of the originally better lung; some, however, were from intercurrent disease.

* Time intervals between operations and publication of reports vary so widely that no attempt has been made to tabulate them; occasionally they are mentioned under "Remarks."

† Classification of clinical results varies greatly according to the individual interpretation of the observer. It is widely accepted, however, that "complete cure" should be defined as freedom from any symptoms of tuberculous activity for at least one and a half years, no sputum, and ability to perform a full day's work.

‡ "Clinical cure" may be defined as freedom from any symptoms of tuberculous activity for at least one and a half years, no tubercle bacilli, but a few cubic centimeters of mucoid sputum, and ability to do a short day's work.

TABLE II.—TOTALS FROM TABLE I PARTITIONED ACCORDING TO TECHNIC EMPLOYED.

Class I*			824
Class II†			200
Total cases			1024
	Class I.	Class II.	Total cases.
Apparent complete cures	205 (c. 25%)	38 (19%)	243 (c. 24%)
Clinical cures	71 (c. 9%)	14 (7%)	85 (c. 8%)
Total cures	276 (c. 33%)	52 (26%)	328 (c. 32%)
Considerable improvements	56 (c. 7%)	39 (19.5%)	95 (c. 9%)
Improvements	159 (c. 19%)	14 (7%)	173 (c. 17%)
Total improvements	215 (c. 26%)	53 (26.5%)	268 (c. 26%)
Total cures + total improvements	491 (c. 60%)	105 (52.5%)	596 (c. 58%)
Worse	32 (c. 4%)	4 (2%)	36 (c. 4%)
Early deaths	102 (c. 12%)	24 (12%)	126 (c. 12%)
Late deaths	143 (c. 17%)	55 (27.5%)	198 (c. 19%)
Total deaths	245 (c. 30%)	79 (39.5%)	324 (c. 32%)
Total worse + deaths	277 (c. 34%)	83 (41.5%)	360 (c. 35%)
Miscellaneous (no change, under treatment and result unknown)	56 (c. 7%)	12 (6%)	68 (c. 7%)

* Patients of the 14 surgeons who were conservative in selecting for operation, and who used standard technic, resecting first rib and sufficient lengths of the others.

† Patients of the 19 surgeons who have not regularly strictly observed conservative standards in selecting cases or who have not regularly performed the complete operation.

Almost every one of the 1024 cases collected in the accompanying tables was desperate, and the disease extensive and severe before operation; almost all had cavity formation and many had bilateral, active lesions, although much worse on one side; almost all had "cured" in sanatoria under competent supervision for one, two, three, five or more years and were unimproved or worse, and in none of them was spontaneous healing to be expected; almost without exception every one was expected surely to die of tuberculosis; artificial pneumothorax had been attempted in all, and had failed because of adhesions. That any appreciable number of such desperately diseased persons could be saved from imminent death is surprising, but that 32 per cent of them actually were cured is almost miraculous. For such cases nothing is known to compare in effectiveness with compression therapy (pneumothorax or surgery), and it deserves the active, aggressive support of every physician and surgeon to whom the tuberculous come for advice.

Conclusions. 1. On account of pleural adhesions many patients with largely unilateral pulmonary tuberculosis do not obtain from artificial pneumothorax the full benefit of lung compression therapy.

2. Many among them are in sufficiently good general physical condition for surgery. The operation of choice is paravertebral thoracoplasty.

3. Any tuberculous lesions in the better lung must be inactive or only slowly progressive, if surgery is to be undertaken.

4. Cauterization, under thoracoscopic vision, of adhesions that are preventing adequate lung compression by pneumothorax should be reserved for those that are long, narrow and few in number.

5. In suitable cases operation should be performed as soon as artificial pneumothorax has proven itself ineffective; procrastination may rob these patients of an excellent chance of complete cure.

6. Thoracoplasty should be done in two stages, from two to three weeks apart. No fewer than 125 cm. of ribs XI to I inclusive should be resected.

7. Local-regional anesthesia is indicated for patients whose daily expectoration is more than 40 cc. When less than 40 cc a combination of nitrous-oxide-oxygen narcosis and local-regional anesthesia is best.

8. The immediate and remote dangers of any operation that compresses only a part of a hemithorax are greater than its advantages, except in unusual cases. This does not apply to a combination of partial thoracoplasty and partial artificial pneumothorax.

9. Neur-exæresis of the phrenic nerve may be performed with advantage before every thoracoplasty and after every artificial pneumothorax.

10. Some stiff-walled apical cavities are not obliterated by paravertebral thoracoplasty. The supplementary operation of parasternal thoracoplasty, or of pneumolysis with muscle, fat, gauze or paraffine "fill" should be considered, but not performed sooner than six months after the primary operation.

11. Some cavities cannot be collapsed, and by retention of secretions cause severe toxemia. Drainage is occasionally indicated for them.

12. Tuberculous empyema is best treated by repeated aspirations and air replacements, and sometimes with antiseptic instillations or irrigations. Only in the presence of dangerous secondary infection may open or closed tube drainage be used. Persistent empyemas, especially if complicated by fistula, often require thoracoplasty for their cure.

13. Favorable results in the surgery of pulmonary tuberculosis depend upon great discretion in the selection of cases, early and skilfully executed complete operations and strict attention to post-operative care, including not less than six months "curing," preferably at a sanatorium.

14. Among 1024 cases of advanced tuberculosis, reported from 1918 to 1923, there was a mortality of 12 per cent during the first month after operation (the immediate operative mortality was about 2 per cent), and 19 per cent thereafter, mostly from tuberculosis in the originally better lung or other organs. Twenty-six per cent were improved, and 32 per cent cured. Of the 824 patients managed according to the criteria given in paragraph 13, immediately above 26 per cent were improved, and 33 per cent cured. Of the 200 cases not so managed 26.5 per cent were improved, but only 26 per cent cured.

A complete bibliography for 1898-1923, inclusive, will appear in the author's reprints.

REVIEWS.

OBSTETRICAL NURSING. A MANUAL FOR NURSES AND STUDENTS AND PRACTITIONERS OF MEDICINE. By CHARLES SUMNER BACON, PH.B., M.D., Professor of Obstetrics in the University of Illinois, Medical Director, Chicago Lying-in Hospital, etc. Second edition. Pp. 324; 126 illustrations. Philadelphia and New York: Lea & Febiger, 1924.

THIS manual presents the theory of obstetrics combined with directions for nursing obstetric patients. It is well arranged, and the scientific side does not over balance the practical. It is simply written, the directions for all nursing procedures are clear, and should be comprehended by the practical nurse as well as by one who has had the advantage of hospital training. For this reason the manual is a good book for the obstetrician as it will better enable him to direct the work of his assistants. A few solecisms remain in the second edition, such as the reference on page 131 to sewer gases from poor plumbing as a source of infection to the parturient.

W.

VENEREAL DISEASE. By HUGH WANSEY BAYLY, M.C., Honorary Secretary, Society for the Prevention of Venereal Disease, London, Eng. Second edition: Pp. 170; 58 illustrations. New York: The Macmillan Company, 1924.

READERS will recognize the author as the leading propagandist in England for venereal disease prevention and a long preface to this book recounts the difficulties and opposition that he has met and overcome as Secretary of the Society for the Prevention of Venereal Disease. His point of view is excellently taken, his arguments are scientifically irrefutable and his fight has made the moralist and religious obstructionist recognize that "intolerable and illogical anachronism that the most easily controlled and most wide-spread and, with the exception of tuberculosis, probably the most deadly of chronic infectious diseases, should be specially selected for exemption from regulations as to prevention, notification, segregation and enforced treatment." The text is short but thorough. The outline of therapy dogmatic but safe, and it should find a place among the books of every venereal officer.

R.

MANAGEMENT OF THE SICK INFANT. By LANGLEY PORTER, B.S., M.D., M.R.C.S. (ENG.), L.R.C.P. (LOND.), Professor of Clinical Pediatrics, University of California Medical School; Visiting Physician, San Francisco Children's Hospital; Consulting Pediatrician, Babies' Hospital, Oakland; Consulting Pediatrician, St. Mary's Hospital, San Francisco; and WILLIAM E. CARTER, M.D., Assistant in Pediatrics and Chief of Out-patient Department, University of California Medical School; Attending Physician, San Francisco Hospital, San Francisco. Second edition. Pp. 659; 54 illustrations. St. Louis: C. V. Mosby Company, 1924.

THE second edition of this work remains a valuable book for the intern and general practitioner. The consideration of the more common symptoms separately, the preciseness of the therapeutic recommendations, the large number of very excellent illustrations, the glossary of formulas and recipes, and the generous list of useful prescriptions, make it a most acceptable book for the man not specially trained. The new edition contains a new chapter on Prematurity and several minor changes. The publishers have succeeded in producing a book highly pleasing to the eye of the reader. S.

L'ANGINE DE POITRINE. By PROF. DANIELOPOLU, Director La Deuxieme clinique medical de l'Université de Bucarest. Pp. 113; 31 illustrations. Imprimerie Cultura, Bucarest, 1924.

THIS 113 page monograph covers the pathogenesis of angina pectoris from the point of view of physiology and pathology. The hypotheses concerning the cause of anginal pain are enumerated and the treatment of this disease is discussed briefly from its medical aspects and fully from the surgical side. An extensive bibliography is given and to one interested in this special topic the monograph is valuable. P.

DISEASES OF THE NOSE, THROAT AND EAR FOR PRACTITIONERS AND STUDENTS. Edited by A. LOGAN TURNER, M.D., F.R.C.S., Senior Lecturer on Diseases of the Ear, Nose and Throat, University of Edinburgh. Pp. 413; 222 illustrations and 12 plates, 8 in color. New York: William Wood & Co., 1924.

THIS present work, written by those engaged in the teaching and practice of the specialty in the Edinburgh Medical School, is in reality a revised and rewritten fourth edition of the text-book by the late W. G. Porter, who was killed in battle in 1917. It is

remarkably thorough, concise and complete for a volume of this size and can be studied with profit even by those far advanced in special work. It is entirely up to date, the illustrations being especially noteworthy for their clearness and their originality. The entire book is well written and printed, and in such a concise manner that practically every subject is adequately treated, even to a description of the anatomy of the parts under consideration. C.

THE INTERNAL SECRETIONS. By ARTHUR WEIL, M.D., Assistant Professor of Physiology at the University of Halle. Authorized translation of the third German edition by JACOB GUTMAN, M.D., PHAR.D., F.A.C.P., Director, Brooklyn Diagnostic Institute. Pp. 287; 45 illustrations. New York: The Macmillan Company, 1924.

INSTEAD of chapter headings entitled "thyroid," "pituitary," "adrenals," etc., which one is accustomed to expect in works upon this subject, one finds in this book chapters upon the blood, circulation, respiration, metabolism, growth, reproduction, etc. This original angle of presentation possesses certain advantages, in addition to which the excellence of the translation, the brevity of the work and its accuracy of statement render it of interest and value to the physician and student alike. A.

FERTILITY AND STERILITY IN HUMAN MARRIAGES. By EDWARD REYNOLDS, M.D., and DONALD MACOMBER, M.D. With a section on the Determining Causes of Male Sterility. By EDWARD L. YOUNG, JR., M.D. Pp. 275; 17 illustrations. Philadelphia and London: W. B. Saunders Company, 1924.

THE chapter on the clinical conduct of a case of sterility is the keynote of the book. It describes with such thoroughness and detail the methods to be used in dealing with the crux of this puzzling medical problem, the diagnosis of the cause, that it may be well singled out for mention in a very readable and well-balanced book.

There is a clear statement of the general biological and physiological problems in the subject as a whole. All the determining causes in the female are taken up in succession. Dr. Young has contributed an excellent section bearing on the aspects of sterility and infertility from faults in the male.

Relative infertility, repeated interruptions of pregnancy, one-

child sterility, the marital habit and the prophylaxis of sterility from pubertal and menstrual hygiene are discussed. Animal experimentation in regard to diet—calcium values and abstraction of vitamins—is referred to with what bearing it may have in the human. Endocrinology is dismissed with a wave of the hand. The final chapter on the surgery of sterility describes various gynoplastic procedures, and gives the authors' conclusions regarding transuterine insufflation of the tubes. W.

HUMAN PHYSIOLOGY: A PRACTICAL COURSE. By C. G. DOUGLAS, C.M.G., M.C., D.M., F.R.S., Fellow of St. John's College, Oxford, and J. G. PRIESTLEY, M.C., D.M., Christopher Welch Lecturer in Clinical Physiology, University of Oxford. Pp. 232; 30 illustrations. New York: Oxford University Press, American Branch, 1924.

THIS is a compilation of experiments which may be performed upon the human subject. Although designed primarily to elucidate physiological principles, the methods used find an application in applied physiology. The laboratory directions are interpolated with the theoretical basis for a proper interpretation of the results obtained.

The course covers the following subjects: Respiration, total energy exchange and energy production, the formed elements of the blood, blood chemistry, blood gases, the polygraph, blood-pressure and the functional activity of the kidneys and the alimentary canal.

The experience of the teachers of physiology during the past ten years has amply demonstrated the value of such a course, which has been advocated for many years in this country by Dr. Yandell Henderson. In addition to its practical value to the medical student, human physiology arouses a keen interest in the student with the result that he retains a more lasting impression of the fundamental physiological principles involved. The possibilities are by no means exhausted in these pages. However, the subjects treated indicate the trend which such a laboratory course may take.

In American laboratories other types of apparatus and chemical methods than those described are in use. Examples which may be cited are the substitution of the Henderson-Haldane apparatus for the original Haldane gas analyzer; the improved Van Slyke methods of blood gas analysis and the Folin-Wu sugar method.

It would seem desirable, wherever possible, in a course which forms the beginning of clinical physiology, to employ methods which the student may have occasion to use in the clinic. G.

DISEASES OF THE EYE. By DR. GEORGE E. DE SCHWEINITZ, Professor of Ophthalmology in the University of Pennsylvania; Ophthalmic Surgeon to the University Hospital; Consulting Ophthalmic Surgeon to the Philadelphia General Hospital. Tenth edition. Pp. 865, 434 illustrations, 7 colored plates. Philadelphia: W. B. Saunders & Co., 1924.

DR. DE SCHWEINITZ has brought his new edition fully up to date in every respect, and it should be in the library of not only every ophthalmologist, but every active practitioner of medicine.

The arrangement and classification of contents makes them easily accessible. The revision has been thorough, so that as a book of reference it is unexcelled, though its real value lies in the interesting detail allotted to every subject of importance.

Among new topics included for the first time are the diaphragm lamp (Gulstrand), contact illumination, binocular visual acuteness, sunlight as a source of illumination in ophthalmoscopy, ophthalmoscopy with red free light, agricultural conjunctivitis, Barraquer's method of suction extraction of cataract, and O'Conner's "Cinch" shortening operation for strabismus. S.

ESSAYS ON THE EVOLUTION OF MAN. By G. ELLIOT SMITH, M.A., M.D., LITT.D., D.Sc., F.R.C.P., F.R.S. Pp. 158; 19 illustrations. New York: Oxford University Press, 1924.

THOSE of our readers who were fortunate enough to hear Professor Elliot Smith on his lecture tour in the United States last spring will need but little introduction to this book. Representing three addresses made to the British Association, the British Academy and the Royal Institution during the past eight years, it contains substantially an elaboration of the matter given in his American lectures.

In the first chapter, "The Evolution of Man," man's pedigree from the remote shrew-like mammal of the cretaceous period is presented together with a discussion of "the factors that were responsible for the emergence of the distinctive characters of man." Professor Smith's view is that the first important step was the adoption of arboreal life with the consequent enormous development of the visual cortex at the expense of the olfactory parts of the brain. With the greater need for precise movements and use of the other senses, this not only developed the motor area but evolved the great prefrontal area "concerned with attention and the general orderly coördination of psychic processes." The assumption of the erect attitude and acquisition of the power of speech are considered

enormously important incidental manifestations of the brain development, which permitted sufficient cortical regulation of skilled movements.

In the second chapter is an interesting description of the various types of primitive man (the Java ape-man, the Piltdown dawn-man, the Heidelberg, Neanderthal and Rhodesian men, and the earliest known varieties of *Homo sapiens*). In the dawn of civilization, the invention of agriculture, and the domestication of the dog and other animals are discussed. The third chapter, the Human Brain, deals in greater detail with the development of the theory already given.

K.

NOTES ON THE MEDICAL TREATMENT OF DISEASE FOR STUDENTS AND YOUNG PRACTITIONERS OF MEDICINE. By ROBERT DAWSON RUDOLF, C.B.E., M.D. (EDIN.), F.R.C.P., Professor of Therapeutics in the University of Toronto; Clinician, Toronto General Hospital; Consulting Physician, Victoria Hospital for Sick Children, Toronto; Fellow of the Royal Society of Medicine; Member of the Association of American Physicians; Ex-Vice-President of the American Therapeutic Society, Colonel, Canadian Army Medical Corps (Reserve), and late Consulting Physician to the Canadian Forces overseas. Second edition. Pp. 486; 4 illustrations. Toronto: University of Toronto Press, 1923.

THIS modest title does not do full justice to the practical excellence of this little textbook of medical treatment, which is full of sound medical philosophy, well written, up to date, and, for the subjects considered, is quite comprehensive. The introduction is a delightful résumé of the history of the science and art of healing. There are 29 additional chapters setting forth in concise form and with a well balanced point of view the modern methods of treating most of the important diseases met with in general practice. The book merits a larger audience than that indicated in the title.

F-H.

DOMICILIARY TREATMENT OF PULMONARY TUBERCULOSIS. By F. RUFENACHT WALTERS, M.D., B.S., M.R.C.P. (LOND.), F.R.C.S. (ENG.), Medical Director, Crooksbury Sanatorium. Second edition. Pp. 288. New York: William Wood & Co., 1924.

THIS book is designed to assist the practitioner as well as the specialist in treating tuberculosis. The addition of two new chapters, one of an introductory nature, and the other on the general topic of home treatment in its public and social aspects, constitute a distinct improvement over the first edition.

A.

SURGICAL PATHOLOGY. By JOSEPH MCFARLAND, M.D., Sc.D., Professor of Pathology in the Medical Department of the University of Pennsylvania. Pp. 701; 435 illustrations. Philadelphia: P. Blakiston's Son & Co., 1924.

DR. MCFARLAND has written a really valuable book—with MacCallum's Pathology and Ewing's Neoplastic Diseases it should immediately take rank as one of the three leading books on Pathology that have been written in English in the past fifteen years. In the preface, he states that the book has been written for those beginning to specialize in Surgery, who "frequently find themselves confronted by problems difficult to solve by recourse to the ordinary sources of information." Valuable as it undoubtedly will be for this class, it will be even more useful—nay, necessary—for their laboratory coöperators, who must give information, diagnosis and prognosis on the surgical tissues brought to them. Particularly satisfactory is the emphasis placed on the normal variations from typical structure, stumbling blocks which not infrequently precipitate the microscopist into the mire of pathological error.

The book is divided into three parts: (1) Congenital Conditions of Surgical Interest (204 pages); (2) Tumors (174 pages) and (3) Special Pathology (269 pages), the bibliography and index taking up the remaining 54 pages. Although the author considers that in this way "the matter has been arranged in logical order and sequence," it introduces certain disadvantages. Thus cholesteatoma, mixed tumors, dermoid cysts, mammary and fetal thyroid adenoma and hypernephroma, having been given under Part I (35 pages), are obviously missing from Part II on Tumors. Also tumors having been considered in Part II, must again be taken up under each organ discussed in Part III, a fault which is of course shared with the textbooks of general and special pathology.

The author states in the preface that he has given particularly full consideration to two kinds of subjects—"those that experience has been shown to be necessary to the student and those concerning which the author has special knowledge." Bearing this in mind, however, the reviewer feels a disproportionate space has been allotted to the congenital (first) part and that various numerous important subjects especially in Part III have been passed without any or with insufficient recognition. For instance, inflammation and infection are nowhere treated systematically, the only abscess indexed being perinephritic abscess. In special pathology, the skin, muscular and circulatory systems are conspicuous by their absence, so that aneurysms, gangrene, ulcers (except of the stomach) and similar important surgical conditions are hunted for in vain. A consistent system governing the inclusion and arrangement of various conditions is manifestly lacking—perhaps purposely so; for instance Myositis Ossificans is listed twice in the index, occurring once in a discussion of metaplasia and once as an "osteomatoid."

As one would expect, the mammary gland is treated fully and ably, as is also a five page discussion of the appendix, but that is no reason why actinomycosis should be mentioned only in these two places. The very fulness of the index offers an easy opportunity for the hasty critic to find such flaws, and yet the system of cross indexing could have been pushed even further to advantage. The spleen is only mentioned for its anomalies (another example of the over emphasis of embryonic defects), while Banti's and Gaucher's diseases and other splenomegalies are completely ignored. While this review was being written, a suspicious tuberculosis of the stomach was submitted for diagnosis. Turning hopefully to the stomach section, the reviewer found no mention of tuberculosis, syphilis or other conditions with which ulcer and cancer could be confused. Starting at the beginning of the index, the reviewer then noted the neglect of abscess, aneurysm, ascites, bedsores, boils, brain lesions, buboes, burns and then desisted.

A few suggestions might be made to the proofreader for the next edition, which will doubtless soon be forthcoming: "Pearlgeschwulst" is an unpleasant hybrid (page 73); "Endodermal" at the bottom of page 72 and "Peal" (page 76) each lack an "r"; Kirmisson, whose name occurs 16 times in the bibliography has acquired an "e" in the text (page 49); likewise Fibiger, the producer of gastric carcinoma in the rat (page 218); "Cordoma" (page 175) lacks an "h," the word "aegagrophilus" (hair ball), if it must be used at all, should always be spelt the same way (page 577 and Index); in the index "Tumors" should come after "Tubular" and "Tuberculosis" and not before; and in the table of contents, the subheadings had better be numbered, if they cannot be properly aligned. These corrections, found in a cursory examination are only samples of many more that indicate the need for a thorough typographical revision.

The illustrations are instructive and interesting and nearly always bring out the desired point. This is more than sufficient excuse for the fact that more than three-quarters are taken from other writers. Of the remaining quarter, many already have been published by the author, a justifiable economy in these days of costly printing. A similar economy in the arrangement of the bibliography, more on the lines of Aschoff, Ewing or Kaufmann, would have either saved considerable space or permitted many more than 700 to be included in the same space. There is also a regrettable lack of completeness in the references given.

It should not be understood from these criticisms, some unavoidable and others unimportant, that the book is not considered a good one. On the contrary, it is a very welcome and valuable addition to pathological literature, and in some respects (as for instance, the clear cut presentation of the first hand views of an expert on the subject), should serve as a model for medical textbook writers. It is on account of its obvious value, that we modestly offer suggestions to make the second edition even better than the first. K.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI,
CINCINNATI, OHIO.

The After-effects of the Late Toxemias of Pregnancy.—HARRIS (*Bull. Johns Hopkins Hospital*, 1924, 35, 103) made a study of 177 obstetrical patients in the Hospital from February 1, 1919, to February 1, 1923. There were 218 deliveries in the series, and 163 of the mothers returned for further study one year after delivery. The main point of value derived from the study lay in facts gained regarding the relation of preëclamptic and eclamptic states to renal disease. Chronic nephritis was found to follow preëclamptic toxemia in a surprisingly large percentage of cases (60 per cent). No way was found, however, to differentiate between the toxemic case that would develop renal disease and those that would not, since the behavior of the blood-pressure following delivery gave no indication. Still if sign and symptoms of toxemia persisted longer than three weeks after delivery, renal disease was always one year later. In fact, with this duration of the toxemia, the presumption is that this underlying disease is renal in origin.

Effect of Tonsillectomy on the General Health of Twelve Hundred Children.—The benefits to children of tonsillectomy become less striking when no selection of cases is made, and when the series is controlled by the same number of similar children with tonsils left intact. KAISER (*Jour. Am. Med. Assn.*, 1924, 83, 33) brings out certain beneficial effects of the operation, however, based on a three-year follow-up study of the control series. Considerable relief is obtained from sore throat, colds, and mouth breathing. The chances for discharging ears and their complication are lessened. The incidence of diphtheria and heart disease was diminished. Malnutrition was definitely reduced following the operation. Chorea or rheumatism, measles and scarlet

fever were equally prevalent in the operated and non-operated series, although the latter two diseases tended to be less severe in the operated cases. No influence was seen on infections of the larynx, bronchi or lungs.

The Vital Capacity of the Lungs and Its Significance in Hyperthyroidism.—MCNEAL (*Arch. Int. Med.*, 1924, 34, 168) has investigated the vital capacity of the lungs in cases of hyperthyroidism. He concludes from his study of a large number of thyroid cases that as a result of the marked reduction of the vital capacity of the lungs, below 70 per cent in a great majority of the severe cases of hyperthyroidism, that this reduced vital capacity points more definitely to a bad prognosis than does the degree of increase in the basal metabolism.

An Insulin-like Material in Various Tissues of the Normal and Diabetic Animal.—Since the discovery of insulin and the extensive researches that resulted have shown that insulin is ubiquitous in nature and is found in all living substances. Additional confirmation of this has been brought forth by BEST, SMITH and SCOTT (*Am. Jour. Physiol.*, 1924, 68, 161) who found that insulin may be extracted from a number of tissues besides the pancreas, although in the pancreas the amount of insulin per unit of weight is much higher in concentration than in other tissues, but in tissues with considerable bulk as liver and blood the total amount is very much greater than the very much smaller organ, the pancreas. These findings together with the findings of insulin-like substances in plants lead the authors to the conclusion that "insulin may prove to be a constituent of every cell in which carbohydrate is metabolized and the islands of Langerhans to be specially developed structures which supply the active material when the demand for it is too great to be provided for by the insulin-producing power of the individual cell."

The Clinical Value of the Serum Tetrachlorophthalein Test for Liver Function.—There is apparently an accumulative mass of evidence which tends to show that the tetrachlorophthalein test for liver function is a valuable procedure, which is not true of practically all the other tests which have heretofore been employed, as they have not proved worthy either because of difficulty of technic in their employment or from the fact that other substances which have been injected into the body as a test of liver function were of no value because they were absorbed from the intestine or excreted by the kidney, making the tests indefinite and inconclusive. In a recent article OTTENBERG, ROSEFELD and GOLD-SMITH (*Arch. Int. Med.*, 1924, 34, 206) have brought together additional evidence to show that the test is of value in certain types of liver disease. The authors use a somewhat larger dose of the drug than it is customary to use but otherwise follow the technic of Rosenthal throughout. They feel from their study of over 100 cases that the test is useful in detecting cirrhoses, metastatic carcinoma, and cardiac decompensation and that its greatest value will probably be in the early diagnosis of these first two conditions. The test is valueless in cases of obstructive jaundice.

Effects of Intramuscular Injection of Sodium Citrate upon Bleeding.—HIGGINS and FISHER (*Ann. Surg.*, 1924, 80, 268), following the experience of Neuhof and Hirschfeld with sodium citrate intramuscularly administered, studied its action on a series of 50 cases of various kinds. They found the maximum effect of the injected salt to occur in about forty-five minutes, and the clotting-time to return completely to normal in one to two days. They report lowering of the clotting-time to about one-sixth its former value, regardless of whether it was previously normal or prolonged. Since the action of the sodium citrate is supposed to be on the blood platelets, causing their disintegration, they advise against its use in cases of purpura hemorrhagica and hemophilia. It has been noticed that, following the transient shortening of the clotting-time in a hemophiliac, there occurred a considerable prolongation beyond that present before the salt injection. Thirty cubic centimeters of a 30 per cent solution of the salt is used, the injection being deep into the buttocks. Novocain injection should precede the citrate solution, otherwise the concentrated salt causes much pain and irritation.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND
ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES
IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SUR-
GEON TO THE PHILADELPHIA GENERAL AND
NORTHEASTERN HOSPITALS.

Actinomycosis.—KEYNES, (*St. Bartholomew's Hospital Reports*, 1924, 72, 71) says that the organism of actinomycosis is a slow, insidious and relentless enemy, whose ravages are often well advanced before its presence is diagnosed. It is certain that purely surgical measures are of first importance and should never be omitted. The seriousness of the disease demands also that every other remedy, which may be supposed to be of value, should be used at the same time. Potassium iodid, which enjoys a reputation founded on long established custom rather than on real success, should be given by mouth in huge doses. Copper sulphate solution should be injected with the lesion. Sinuses should be irrigated with the same solution. Autogenous vaccines should be given as soon as the organism is isolated. Roentgen-rays should be given in deeper lesions, radium to the superficial.

Compression Leverage Fractures of the Ankle Joint.—STEVENS, (*Am. Jour. Surg.*, 1924, 38, 134) says that these leverage fractures of the ankle under compression are all of the same etiology and vary simply from distribution of force and intensity of stress. This applies to most of the so-called simple fractures of the lower end of the fibula, since the salient features of this fracture are present, *i. e.*, ligamentous and tendon

injury and a destroyed mortise, permitting dislocation. Fractures of the inversion type are not usually attended with so great a destruction of ligaments, but there is an equal or more serious involvement of tendon sheaths and a greater posterior dislocation is common. The author feels that the majority of these ankle fractures are not tremendously serious injuries and do not deserve the bad repute, which is theirs at present. Motion, active and passive, from the very beginning is the solution of the problem. No masseur is competent to remedy any bad result, while in the hands of a man who understands the pathology of the lesion there is no danger.

Appendectomies at the Lankenau Hospital.—DEAVER and MAGOUN (*Ann. Surg.*, 1924, 79, 854) say that acute appendicitis is, in the majority of instances, a disease of early adult life, although it may occur at any age. The mortality in this disease has decreased practically 50 per cent during the last decade and while the general increase in knowledge concerning it may partially account for this, it would seem as if the expectant treatment of spreading peritonitis is also of value. After the peritonitis has localized and a mass is present, the incision as described will be of value in the extraperitoneal approach to the ileum. In practically every case the appendix is removed, drainage varies with the situation of the abscess. Cigarette drains and pieces of gauze are commonly used, and occasionally as in pelvic abscess a glass tube is used. The highest mortality follows subdiaphragmatic abscess or multiple abscess. If the cecum or ileum is indurated or ulcerated at the primary operation, fecal fistula will occasionally occur. When the appendix with the abscess lies under the terminal ileum, obstruction may follow.

Two Hundred and Sixty-two Consecutive Cases of Appendicitis.—GOTCH and DURMAN (*Ann. Surg.*, 1924, 79, 862) say that appendicitis is probably the most important and frequent surgical disease. About 14,000 people die annually from it in the United States. The death-rate for the present series was 7.2 per cent, while 205 cases complicated by abscess had a death-rate of 9.2 per cent. The preoperative intravenous injection of normal saline solution is advocated as a treatment for all very sick patients. The advantages of the McBurney incision are pointed out. The expectant treatment of appendicitis is not advised. The postoperative treatment consisted of the administration of plenty of fluid, by the intravenous route, if water could not be taken by mouth; sufficient morphin; starvation until peritonitis had completely subsided; and frequent examination for secondary abscesses and prompt drainage of the same.

Early Gall-bladder Pathology.—DEAVER and RIESMAN (*Therap. Gaz.*, 1924, 48, 381) say that they have noted the strong resemblance between the symptoms of lesions in the gall-bladder and the symptoms of what later proved to be chronic appendicitis. On the other hand the senior author has had the experience of finding that appendectomy may fail to relieve a patient of his digestive troubles and on reopening the abdomen, the actual site of disease is found to be the gall-bladder. This error in diagnosis is entirely pardonable, because the differentiation in

an appendix, particularly when it is in a high position and cholecystitis cannot always be made clinically, and in addition, even with a good exposure in an opened abdomen, the presence of cholecystitis may be doubtful. Cholecystic adhesions do not always indicate a diseased gall-bladder, but they arouse that suspicion. Next to disease of the gall-bladder the most common upper abdominal disorder is duodenal ulcer, which in the senior author's experience rarely has given rise to adhesions. Therefore the presence of cholecystic adhesions may be taken to indicate not duodenal ulcer, but cholecystitis or possibly appendicitis.

Hepatitis—A Condition Associated with Gall-bladder Disease.—HEYD (*Surg., Gynec. and Obstet.*, 1924, 39, 40) says that hepatitis in some degree is almost invariably associated with chronic disease of the gall-bladder and biliary ducts. Hepatitis may exist as the primary or secondary lesion. When hepatitis is the primary lesion, infection takes place through the portal system with secondary infection of the gall-bladder, by way of the lymphatics. When hepatitis is the secondary lesion, infection takes place from the gall-bladder by way of the extra-hepatic and intrahepatic lymphatics. In the majority of cases, the hepatitis is probably symptomless; it may occasionally be sufficiently widespread to initiate changes leading on the one hand to types of biliary cirrhosis, and on the other hand to types of portal cirrhosis. Cholecystitis may be secondary and of minor importance to changes in the liver. Some cases after operation show a marked degree of hepatic insufficiency. The liver, pancreas, gall-bladder and gastroduodenal segment, must be viewed as one physiological and pathological system, disease of one organ expressing itself in varying degrees of pathological change in the other members of the group. Pancreatitis is a frequent concomitant in either hepatitis or biliary system infection. In hepatic insufficiency or hepatic dysfunction, we find marked variations in blood chemistry.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,
NEW YORK.

Further Experiences with the Insulin Treatment of Diabetes.—Having used insulin for about one year in their private clinic VON NOORDEN and ISAACS (*Klin. Wchnschr.*, 1924, 17, 720) report that during the last half year the daily number of insulin injections has increased to about 2000 units a day. Since using insulin they have not lost a case from diabetic coma, and consider that the most striking results are obtained in the cases of precoma and coma. The prognosis of coma cases which were formerly treated with strict starvation and large doses of alcohol has been increased 50 per cent. Their most severe case of coma

required 100 units in twenty-four hours. Usually 30 units given at three-hour intervals are sufficient in these cases. Careful observation of the patient for symptoms of hypoglycemia, and observance of the blood-sugar curve should be made, and a dextrose infusion at hand to be given if necessary. In small diabetic children periods of marked acetonuria may appear between the periods of freedom from glycosuria and acetonuria. These are due to acute nutritional disturbances similar to the cases of acidosis with vomiting seen in children, and can be controlled with small doses of insulin. The smallest dose of insulin which will give the desired results should always be used. Eighty to 100 units a day may be necessary for a time, but usually 40 to 60 units is sufficient. Their routine insulin and diet treatment is: 1. Two test days when the patient receives 1 to $1\frac{1}{2}$ gm. of protein per kilogram of body weight, and 100 gm. of bread; then, (2) a bed and fast day; then, (3) a bed and egg day when five eggs and 300 to 400 gm. of green vegetables or salad, and 80 gm. of fat are allowed. (Usually the urine is sugar-free or nearly so by this time.) 4. A strict diet with small doses of insulin night and morning is then begun, and the diet is gradually increased with the addition of carbohydrates, fat, and protein depending on the amount of insulin required and the condition of the patient. 5. Every five or seven days either a fast, egg, or vegetable day is required; when the morning dose of insulin only is given. 6. This test diet is not concluded unless the patient has reached a diet which he can continue at home. At least 80 to 100 gm. of bread, or its equivalent, and about 1 to 2 gm. of protein per kilogram of body weight. After two to three weeks of insulin treatment the intolerance to albumen has become much less than that to carbohydrate so that the test diet may include five to six days of diet rich in protein and fat and poor in carbohydrate. In this way the amount of insulin may be reduced. This increased tolerance for albumen is a great advance in the management of diabetics, for years of observation have shown that a protein-poor diet is desirable in reducing a glycosuria, but bad for the patient. When the patient has gained in weight and strength, and is sugar-free and acetone-free he may continue at home. a. Continuation of the diet on discharge with not more than two insulin injections a day. b. In order not to let him become habituated to the insulin a carbohydrate-free day every week is given, with only one small insulin injection in the morning. c. Usually each week a fast, vegetable, or egg day is ordered and the next morning the blood sugar may be so low that the insulin can be omitted. Fast days are not often ordered, and egg days are better than green vegetable days. Periods when the patient may be refractory to insulin treatment must be recognized. In these cases insulin should be tried again after a week's interval. Whether the so-called "severe cases" seen in children, young adults and sometimes in later years will be as greatly benefited by insulin as some American physicians believe, is still undecided. The moderately severe cases are the most successfully treated, and because of insulin more liberal diets can be given, the patient has more strength, energy, and feeling of well-being, and the future for him is more assured. They believe that a 25 per cent advance has been made in the treatment of this type of case over the former dietetic treatment alone, although with the insulin treatment the diet must be more strictly followed than before.

The Basis of Allergic Phenomena.—HANZLIK (*Jour. Am. Med. Assn.*, 1924, 82, 2001) divided allergic phenomena into two classes: (1) The anaphylactic, and (2) the anaphylactoid. The former require a native or complex protein for their production as well as a period of incubation; while the latter can be produced by a great variety of agents unrelated physically or chemically, and no period of incubation is required. The symptoms of both are nearly identical although protein anaphylactic phenomena are characterized by a hyperexcitability of smooth muscle, and both phenomena appear to rest on a common basis, namely, on disturbances in the physical and colloidal mechanisms of the blood and tissues. The result of these changes is the alteration of physical functions ordinarily recognized as "reactions." That there is a mutual relationship between these reactions and pharmacological phenomena is evident and of broad significance in biology. Numerous pharmacological analogies can be given to show how drug action varies with the functional state of the organ or organism, and how a drug may have its ordinary action inhibited or reversed by previous alteration of ionic equilibrium. In the treatment of disease empirical use has been made of a great variety of substances which produce anaphylactoid phenomena. Usually diseases of unknown etiology are so treated, and the beneficial results often obtained probably depend upon the alteration in cellular function with increased capillary permeability which would aid in the removal of edema and chronic inflammations, and facilitate exchange of metabolites, increase the metabolism, etc. On the other hand the results may be alarming and even result fatally. There is no justification for the intravenous use of such agents as hexamethylene, iodid and salicylate because their ordinary systemic effects are readily and promptly obtained from oral administration, and their intravenous administration is followed by definite chemical and physical changes which indicate that they are disturbing and injurious to important functions and tissues. An agent injected intravenously may be temporarily beneficial to one function, but detrimental to others and to the organism as a whole, and the intravenous effect can not be predicted from the physical or chemical properties or from their pharmacological effects when given by mouth.

The Thyroid Treatment of the Nephroses.—Though CAMPANACCI (*Wien. med. Wchnschr.*, 1924, 11, 257) assumes that the action of thyroid extract on general metabolism is well known he reviews briefly the facts which various workers have discovered regarding its diuretic action, and outlines the beneficial results which he obtained by the administration of thyroid extract to 3 cases of nephrosis. Following the researches of Eppinger who first emphasized the relationship between the thyroid gland, diuresis, edema, and kidney function and showed that thyroid extract played an important part in the mobilization of salt and tissue protein it was recognized that the kidney alone was not the only important factor in the question of diuresis but that the tissue spaces of the entire body played an equally important part. Eppinger considers thyroid extract to be a diuretic with an extrarenal action, and an ideal agent in those cases where the usual diuretics cause too severe irritation of the kidney. He particularly recommends its use in cases of myocarditis and in cases of nephrosis, and recognizes

a complementary action when used in conjunction with digitalis. Eppinger advises a beginning dose of 0.3 gm. of the desiccated thyroid extract gradually increasing to 1.2 to 1.8 gm. a day. If no results are seen at the end of two weeks' administration it can be discarded as useless.

Regarding the Cause and Treatment of the So-called "Mucous Colitis."
 —WENT (*Deutsch. med. Wchnschr.*, 1924, 20, 632) outlines the successful vaccine treatment of 9 cases of mucous colitis. He believes that the intestinal tract of these cases has lost its inherent protective mechanism against bacterial invasion and their products, and that the resultant inflammation causes the symptom-complex known as mucous colitis. After examination of the fecal flora of his cases he does not believe that the streptococci play an important part in the etiology of mucous colitis, but does believe that the colon bacillus through a lowered resistance of the intestinal wall becomes an important factor. He prepares vaccines from the patient's stool by growth on endo-agar for twenty-four hours, then transplants are made to plain agar slants which are grown for twenty-four hours and suspension of the growth is made in 15 cc of saline solution. Growth is killed by heating at 56 degrees, and 0.5 per cent carbolic acid is added as a preservative. One-half cubic centimeter is injected subcutaneously, and two days later 1 cc and then two days later 2 cc.

The Raw Fruit Cure.—MENDEL (*Klin. Wchnschr.*, 1924, 15, 624) considers that the successful handling of severe disturbances of circulation with the Karell milk diet depends on the diminution of the fluid intake and the low sodium chlorid content of milk rather than on its diuretic action or the absence of irritating substances. In cases of edema due to cardiac or renal insufficiency as also in many other diseases such as acute nephritis, gout, acute eczema, etc., he advocates a diet of raw fruit in place of a Karell diet. Not only is raw fruit more acceptable to most patients, but excellent results were obtained as the sodium chlorid content of fruit is negligible, and the albumen content only 0.3 per cent. In most cases 1 kilogram of raw fruit a day is enough to satisfy hunger and thirst, and rest in bed during this diet as with the Karell diet is necessary.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
 OF PHILADELPHIA.

Thymus of New-born, and Its Significance to the Obstetrician.—PETERSON and MILLER (*Jour. Am. Med. Assn.*, 1924, 83, 234) observed that abnormally enlarged thymus is common in the new-born, occurring in from 40 to 50 per cent of such infants. In general few symptoms indi-

cative of thymic hyperplasia are apparent the first day of life. When these do occur they are usually mild. A tendency to higher rate of thymic hyperplasia is noted in infants born of elderly mothers and of multiparas, in male infants and in infants born at term. No appreciable difference in size or weight exists between infants showing thymic hyperplasia and those with negative thymus. There is a definite fluctuation in the size of the thymus synchronous with respiration. From a diagnostic standpoint the roentgen-ray is superior to clinical methods in arriving at an estimation of the size of the thymus. While it may be impracticable outside of a hospital to subject every new-born infant to the roentgen-ray, it is absolutely essential that every baby with thymic symptoms be so treated. Stereoscopic films of the chest taken at the end of expiration are of more practical value than fluoroscopic observations. Potential dangers from hyperplasia of the thymus may be eliminated by early diagnosis and by roentgen-ray treatment. This treatment is fairly well standardized. At a focal distance of 12 inches with a three-millimeter aluminum filter interposed the exposure is made for two to three minutes. This is less than one-half an erythemic dose. Three treatments of this character are given at intervals of one week.

Exsanguination-transfusion in Treatment of Severe Toxemia.—ROBERTSON (*Arch. Surg.*, 1924, 9, 1) advances a treatment of toxemias that was suggested during the war. Experimentally very encouraging results were encountered, but clinically it is recognized that in profound toxemias the employment of blood-letting followed by transfusion was ineffective owing to the relatively small amount of the total quantity of blood removed and replaced. As experience with this method increased it was recognized that the more complete the replacement of the patient's blood with fresh blood, the greater the effect on the toxemia and the greater chance of the improvement being permanent. The principle of the operation is to withdraw blood from the median basilic vein of the donor or donors into 100-cc glass syringes, each of which contains 10 cc of freshly prepared 3.5 per cent sodium citrate solution. A quantity equal to the total circulation of the individual is thus obtained. In estimating the amount required it is considered that the quantity of blood in any patient's circulation is roughly 35 cc per pound of body weight. The cannula for the transfusion is first introduced and tied in a suitable vein, such as the internal saphenous at the ankle or the median basilic at the elbow, and salt solution is slowly introduced to prevent clotting. The exsanguination cannula is then inserted. In small infants, the superior longitudinal is made use of for exsanguination, but in children in whom the anterior fontanelle is closed the femoral vein provides a suitable substitute. Blood is withdrawn from the patient until signs of exsanguination begin. The amount that can be withdrawn from small children varies from 60 to 160 cc. With the first sign of weakening pulse, one of the 100-cc syringes containing citrated blood from the donors is connected with the cannula and the introduction of fresh blood is begun. After transfusion has been begun, introduction and withdrawal of blood are kept up at the same rate until all the available blood has been transfused. The beneficial effect of this procedure in certain profound toxemias and septicemias has been demonstrated clinically on a great many occasions.

In cases of severe superficial burns, in which the symptoms indicate a possibly fatal result, exsanguination-transfusion has reduced the mortality from 100 to 50 per cent. In erysipelas of the new-born, the mortality has been reduced from nearly 100 per cent to 50 per cent, and in patients from one month to twelve months of age, it has been reduced from 50 to 13 per cent. In acute septic scarlet fever, the method seems to be of decided value in tiding the patient over the period of intense intoxication as well as converting the case into one of the ordinary type. In acute intestinal intoxication the procedure has reduced the mortality from 20 to 25 per cent of the former rate. The results in septicemia are somewhat disappointing. Although there was marked response in some cases, the benefit seemed to be slight and temporary. This was especially the case in staphylococcus infection and in endocarditis.

The Mechanism of Infection and Immunity in Congenital Syphilis.—KOLMER (*Atlan. Med. Jour.*, 1924, 27, 707) states that in fully 90 to 95 per cent of cases evidences of syphilis will be found in the mothers and the infection is probably a direct one of the children by placental transmissions of *Spirocheta pallida*. It may be argued that the placenta is well known to be a filter of organisms and that the child in the uterus very commonly escapes infection during septic or other infections of the mother, but the *Spirocheta pallida* is an exception and by reason of its ability to infect the smallest perivascular lymph spaces is enabled by this biological quality to break through the placental barriers capable of restraining streptococci, pneumococci, tubercle bacilli and the like. Small-pox is another exception that the placental barrier does not stop. In the majority of cases it appears that *spirocheta pallida* is transmitted to the fetus during the spirochetemic stage of syphilis of the mother. Just prior to and during the clinical secondary stage of syphilis of the mother spirochetemia is most marked, and infection of the child is consequently most likely to occur at this time of the pregnancy, but even during the later years of syphilis, temporary periods of spirochetemia develop with transmission of *Spirocheta pallida* from old foci to new tissues and organs of the mother and it is possible for the *spirocheta* to invade the new tissues of pregnancy including the fetus. It is also possible for conception to occur and pregnancy to terminate at full term without infection of the placenta or child during the latent periods of syphilis of the mother, especially after repeated pregnancies have thrown her syphilis into extreme stages of latency. Infection of the child depends on whether or not anything disturbs this latency of the mother, with the production of spirochetemia. If this occurs the child will become infected, but if it does not occur the child will escape. Except for the danger of congenital syphilis, pregnancy could be regarded as a therapeutic measure of value for the mother since it greatly increases her immunity and tends to protect her against the development of old lesions and the production of new ones especially in the tissues of the central nervous system.

Cause and Treatment of Otitis Media.—SMITH (*Am. Jour. Dis. Child.*, 1924, 28, 1) found in 613 admissions 33.4 per cent of the children had otitis media when they came in or developed it in the hospital. The race and sex of the patient seemed to have no influence of the incidence

of the disease. There was a definite seasonal variation. In February 47.3 per cent of the patients had otitis media. In July only 23.6 per cent were attacked. The most susceptible group was between the ages of three and fifteen months. In this group 50 per cent of the children had otitis media. Patients with pneumonia, dysentery, nasal diphtheria, pertussis and pyelitis developed otitis media in 50 per cent or more of the cases. Those with prematurity, nephritis and the non-infectious diseases showed ear infections in less than 21 per cent. Hemolytic streptococci were isolated from the aural discharge in 56 per cent of the cases cultured. The average duration of the disease was twenty-five and a half days. He found that practically all the Gram-negative bacteria found in the ears of patients suffering from otitis media except *B. pyocyaneus* are killed by an 0.5 per cent solution of sodium hydroxy-mercuri-benzo-phenone sulphonate. *B. pyocyaneus* are readily eliminated by treatment with 2 per cent acetic acid or preferably with 0.5 per cent of the sodium solution that contains 2 per cent of acetic acid. All the Gram-positive bacteria found in otitis media are readily killed by gentian violet except streptococci. Neutral acriflavine has been proved to be more potent in the treatment of otitis media associated with streptococci, but even this drug is not entirely satisfactory. Twenty cases of chronic otitis media were cured by local chemotherapy in an average of seven days each. Sixty cases of otitis media were cured in an average of thirteen days each.

Roentgen-ray Studies of Stomach Function.—ROGATZ (*Am. Jour. Dis. Child.*, 1924, 27, 53) undertook his work in order to study the various functions of the infant stomach, about which there was a marked divergence of opinion in the scant literature. Fluoroscopic examinations and roentgenograms of the stomach were made at regular intervals before and after meals, with observations concerning form, size, position, air bubble peristalsis and emptying-time. Three types of feeding were used with each child; milk diet of average caloric value; a concentrated milk; and a gruel or mush of thick consistency. A gruel or cereal made with milk, no matter how thick it was before ingestion, becomes fluid in the stomach under the influence of the saliva and body heat, whereas a food of mashed potato or vegetable mush retains its consistency. The empty stomach is difficult to see with the fluoroscope. The filled stomach is clearly visible without contrast mediums and lies in the upper, left quadrant of the abdomen, close to the diaphragm, extending in a horizontal plane to or just beyond the midline. The stomach shadow on the plate may be defined by an upper, deeply shaded portion due to the air bubble, and a lower, less intensely shaded area which is the stomach contents. The air bubble varies in size, shape and form in all stomachs, with fluid content, but it is distinctly smaller, or often absent, when thick gruels are swallowed. There are two main, constant types of stomach with fluid feedings. Both are horizontal and extend to or just beyond the vertebral column to the right. One shape is that of a pear or a flask lying on its side, with a large circular expanded fundus and a smaller, narrow pyloric area. The other occurs less frequently and is smooth, elliptical or oval in shape. A third form may appear in either of the first two types when thick gruels are ingested. This is a small circular or oval form, about one-third the size of the fluid forms, with little or no air bubble.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY AT THE SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA.

An Experimental Study of the Etiology of Herpes.—MARIANI (*Arch. f. Derm. u. Syph.*, 1924, 147, 259) publishes with a full bibliography the results of an extended experimental study of various forms of herpes, including simple febrile, progenital, aphthous and zoster types. He regards the various clinical forms of herpes as merely variations on a fundamental reaction process whose clinical differentiation is merely of relative importance. The fundamental fact in the pathogenesis of herpes is an injury to the nervous system, by direct or indirect infection, exogenous or endogenous toxic, or traumatic agents. Existing theories of the mechanism of this action are so complex, indefinite and unsatisfactory as to offer little tangible basis for study. The author frankly states that the same causes, acting through the nervous system may in one case produce simple and in the other zosteriform herpes. Mariani attacks the etiologic problem by inoculation of rabbits with the fluid from unbroken herpetic vesicles, obtained under precautions against contamination and with suitable controls drawn from other bullous or vesicular non-herpetic dermatoses. His conclusions are summarized as follows: Herpes zoster is not autoinoculable and cannot be transferred from person to person in man. Cutaneous inoculation is likewise negative in rabbits and guinea-pigs. Corneal inoculation in guinea-pigs is likewise negative. But in rabbits a form of keratitis may be induced by the vesicle fluid. In febrile or simple herpes, such inoculations on the rabbit's cornea were almost invariably positive, giving rise to a distinctive form of keratitis which did not occur with other vesicle fluids used as controls. The keratitis thus induced in rabbits followed a typical course, regardless of the source of the material, which was obtained from herpes occurring in a wide range of febrile diseases. This herpetic keratitis was inoculable from animal to animal, retaining its clinical and pathologic characteristics but with occasional inexplicable attentuations or accentuations of the virulence of the virus in successive inoculations. Filtered material from herpetic keratitis gave positive inoculations with milder manifestations in fresh animals. Cutaneous and intramuscular inoculations failed uniformly. After intravenous injection of the material, positive results could only be obtained by previously scarifying the cornea. It was observed that herpetic keratitis might develop in the uninoculated eye, and in these cases an infiltrative perineuritic process affecting both eyes by way of the optic nerves and chiasm was recognized. In other animals, both after inoculation from man and from other animals, symptoms in the nervous system constituting apparently a form of encephalitis developed, terminating fatally in many cases in from three to five days. The onset of the encephalitic syndrome was usually on about the tenth day after

the first appearance of the keratitis. Histologically it was possible to demonstrate in these cases, both a meningeal phase, and degenerative changes in the nerve cells. Subdural inoculation of rabbits with filtered or unfiltered brain material from animals with "herpetic" encephalitis, produced encephalitis, and encephalitis could likewise be directly induced by inoculation of filtered or unfiltered material from herpetic keratitis. This was especially true if the source of the herpetic fluid was a rabbit infected from a patient with lethargic encephalitis. Simultaneous inoculation of both rabbit corneæ led to bilateral keratitis. If only one cornea was inoculated the other cornea remained susceptible for about twenty-five days, after which an immunity or resistance to inoculation developed lasting about eighty days. Inoculation with zoster material did not confer any more prolonged immunity than that from ordinary herpes notwithstanding the tradition of prolonged immunity following attacks of zoster in man. No immunity against herpetic keratitis was conferred by other modes of inoculation of the virus in rabbits, nor were any drugs found whose use protected against corneal inoculation of the virus. The existence of a syphilitic keratitis did not protect the involved cornea from inoculation with the herpetic virus. Inoculation of saliva from patients with herpes, and of spinal fluid from a patient with severe meningitis whose febrile herpes produced a sharp herpetic keratitis in rabbits, gave negative results. It was possible to obtain keratitis-producing material from the intracutaneous tissues of herpes carriers, but no inoculation from rabbits to man could be obtained. Progenital herpes of many varieties gave almost invariably positive inoculations on the rabbit cornea, differing in no important particulars from that produced by febrile herpes. A few examples of herpetic keratitis from herpetic aphthous lesions were also obtained. The cultural studies of herpetic material yielded staphylococci, pseudodiphtheroids and a Gram-positive diplococcus. No reactions on the cornea could be obtained from these cultures except in the case of *S. albus*, in which case a purulent ulcerative keratitis differing from the herpetic type developed. In his critical discussion the author concludes that herpes zoster is not an etiologic entity. The infectious character of herpes in general is regarded as presumptively established. The virus has apparently a special affinity for the nervous system and for epidermal tissues, the two factors being inversely related, and one or the other coming to the fore under varying conditions. The virus is regarded as filterable one, capable of producing both herpetic lesions and encephalitis. Many of the clinical manifestations of herpes are due, not to the virus but to subsequent secondary infection with other organisms. The author dwells upon the wide variability in virulence of the virus which in some cases give rise merely to benign herpes and at the other extreme, to grave encephalitic manifestations, and points to the possibility that investigations such as his may have a bearing on the etiology of encephalitis lethargica and molluscum contagiosum.

Skin Resistance to Ultraviolet Light.—MAYER (*Arch. f. Derm. u. Syph.*, 1924, 147, 238) concludes as the result of an experimental study that increase in pigment is not a necessary factor in the development by the skin of resistance to ultraviolet light. Vitiliginous depigmented

areas under exposure to ultraviolet light undergo the same reduction in susceptibility to turpentine and cantharides as do pigmented areas.

Gold Sol Reaction.—PICK (*Arch. f. Dermat. u. Syph.*, 1923, 144, 105), in a series of studies of the gold sol reaction in syphilitic spinal fluid states that the changes are highly characteristic for syphilitic fluids. Too much emphasis cannot be placed on the questionable reactions which persist at times after treatment. He observed paretic gold sol curves in staphylococcic meningitis, endothelioma of the dura, and tumor cerebri.

Keratosi Blennorrhagica from Roentgenotherapy.—OELZE (*Arch. f. Dermat. u. Syph.*, 1923, 144, 1) reports a case of keratosi blennorrhagica apparently provoked by roentgen-ray treatment applied to a gonorrheal joint for the relief of pain. A large group of keratotic lesions appeared at the site which had been subjected to the radiation and other quite characteristic lesions appeared upon the toes. A careful search was made for the gonococcus in the lesions with negative results, a finding in accord with that in the literature at large.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, MEDICAL SCHOOL, UNIVERSITY
OF PENNSYLVANIA, PHILADELPHIA.

Results of Radiation on Cancer of the Cervix.—The literature of today is pregnant with articles relative to the use of radium in the treatment of cancer of the uterine cervix. A close scrutiny, however, shows a real scarcity of reports of the results of any large series of cases of cervical cancer treated by radium after the crucial five-year period has passed. Therefore it is particularly interesting to note a report of the cases treated at "Radiumhemmet," Stockholm, which has been written by HEYMAN (*Jour. Obstet. and Gynec. of the Brit. Emp.*, 1924, 31, 1) and which deals only with cases of carcinoma of the cervix. "Radiumhemmet" is a hospital founded by the Cancer Society of Sweden and partly supported by the Government, which was especially established for the radiological treatment of gynecological cases. Surgical treatment is only employed as an adjuvant to the radiological treatment. In cases of carcinoma of the uterus radiological treatment only is practised. The patients are referred for treatment to "Radiumhemmet" almost exclusively by surgeons or gynecologists, mostly from hospitals and gynecological clinics. As a rule, only three applications of radium are made. The second application is made one week after the first and the third application three weeks after the second. If possible, radium

is applied at each treatment both in the vagina and in the uterus, the length of time of each application being twenty-two hours, using from 33.7 to 40.1 mg. in the uterus each time, making a total dosage of about 2220 to 2640 mc. hours. In the vagina 70 mg. is used three times, making a total dosage of about 4500 mc. hours. The radium is always filtered through 3 to 4 mm. of lead. During the last three years a more concentrated treatment has been tried, the number of applications being reduced to two, thirty-two and twenty-four hours respectively. In such cases the total vaginal dose has been limited to 4000 mc. hours. All operative interference at the commencement of the treatment, such as cauterization or excochleation, is absolutely contraindicated and the treatment is never repeated within the first six months. If, six months after the three applications already mentioned, the growth has not disappeared or if there is a recurrence, the treatment may be repeated, though *preferably* not until a year after the first treatment and only one application is then made. Clinically healed patients, as well as patients with a suspected "reactive" inflammation, are not treated again until a recurrence has been definitely proved. If there is a local recurrence and the growth is operable, hysterectomy is performed. If there are extensive glandular metastases roentgen irradiation is used in conjunction with the radium treatment. It is also used if severe pains persist after the radium treatment and if there is a recurrence in the parametria. This report covers the period of eight years from 1914 to 1921, during which time 505 cases of cancer of the cervix were primarily treated. From 1914 to 1918 the inoperable and borderline cases constituted 91.2 per cent of the series, but from 1919 to 1921 these cases constituted only 68.4 per cent. One-third of the patients were under forty-six years of age; 19.1 per cent were forty years of age or under. In the statistics which follow, all the patients who have died have been counted as dying from cancer.

Operable or Borderline Cases:

1914-1918	40.5 per cent free from symptoms after 5 years.
1919	47.3 per cent free from symptoms after 4 years.
1920	60.0 per cent free from symptoms after 3 years.
1921	58.3 per cent free from symptoms after 2 years.

Inoperable Cases.—1914-1918. 16.6 per cent free from symptoms after five years. Of the remainder 20 to 25 per cent, varying with the year, were free from symptoms after three years. Heyman has observed that if local recurrence occurs, as a rule it does so within one year, but glandular recurrence and metastases may supervene after years of apparently good health. Pain, anemia and fever nearly always indicate the presence of cancer in the pelvis. The complications due to radium treatment are chiefly rectal, which appear as a rule, six months after the treatment, and are due to overdosage and include tenesmus and hemorrhage. Since 1915 he has not had a case of fistula, while 5 patients died of diffuse peritonitis and sepsis as the result of the treatment and one from pulmonary embolism. The primary mortality in this series is 1.19 per cent.

Nature of Uterine Secretion.—In his recent contribution to the literature, KROSS (*Am. Jour. Obstet. and Gynec.*, 1924, 7, 310) recalls his previous experimental work which we have already quoted, showing that the uterine secretion in the rat was able to increase, to a marked

degree, the coagulation period of blood taken from rats, guinea-pigs, and man. In addition to this property, the mixture of uterine secretion and blood after its coagulation, became fluid, as a result of a fibrinolytic ferment present in the uterine secretion. The findings of the above experimental investigation of uterine secretion in the rat taken in conjunction with the phenomenon of menstruation, seemed to point to the solution of the problem of the incoagulability of menstrual blood. It is fair to assume that the menstrual blood is mixed with the uterine secretion as it passes through the endometrium, and that the uterine secretion interferes with coagulation by delaying it sufficiently to allow the fibrinolytic ferment to dissolve any of the small clots that may form. In order to prove that there exists in the human being a uterine secretion similar to that found in the rat, Kross employed the hematocolpos fluid obtained from one of the patients in the gynecological ward of the Mt. Sinai Hospital. The patient, aged sixteen years, presented the typical picture of an imperforate bulging hymen with a history of amenorrhea with periodical monthly attacks of pain in the lower abdomen for a year. The hymen was incised under aseptic precautions and the thick tarry accumulation of old menstrual blood was carefully saved. About 10 cc of this fluid were mixed with an equal quantity of blood taken from the median veins of other patients. A control specimen of unmixed blood was also taken in every instance. The hematocolpos fluid was in this way tested with the blood of seven other individuals and in every instance there was a marked increase in the coagulation period. The nature of the clot formed by the mixture of the two bloods differed very distinctly from that formed by the control blood. In the former, the blood clot was much softer and much more jelly-like. The tubes containing the mixed bloods and those containing the control bloods were then placed in the incubator. After a period of time varying from one-half to four hours, it was noted that the clot formed in the mixture became softer, and finally in four instances became completely fluidified. In the other instances, the fluidification was almost complete and the residual clot very small and extremely soft. The clots in the control tubes on the contrary, became progressively harder and showed absolutely no tendency towards fluidification. From these results, Kross believes that it is fair to state that the hematocolpos fluid is thoroughly mixed with uterine secretions that contains a fibrinolytic ferment similar to that present in the rat and that its fluid nature is due to the action of this ferment. Similarly it can be stated that in the normal individual, the menstrual blood is fluid and that it does not clot subsequent to its escape from the uterus and vagina, as a result of the activity of this ferment. Where the menstrual fluid is composed of more or less clotted blood in an individual whose internal genitalia are not the seat of an abnormal anatomical change, it seems proper to conclude that in that case there is a deficiency of this fibrinolytic or thrombolytic ferment.

A Modified Gilliam Operation.—The operation which LEICESTER (*Jour. Obstet. and Gynec. of the Brit. Emp.*, 1924, 31, 68) describes as an improvement on the classical Gilliam procedure is performed by opening the abdomen through a transverse incision. After incising the skin and before dividing the aponeurosis, the lower flap is carefully dissected from the aponeurosis in a downward direction until both the

external abdominal rings are exposed and clearly defined. After the peritoneal cavity is opened, the uterus is pulled up, and a silkworm gut suture is passed around each round ligament and tied not less than three-quarters of an inch from its attachment to the uterus. A Lucas nephrectomy needle is then passed into each external abdominal ring, along the inguinal canal and then inward parallel to the round ligament, under the peritoneum of the broad ligament, until the site of the ligature is reached. During this process the round ligament is kept taut by an assistant pulling on the ligature. The needle is then made to emerge through a nick made with a scalpel through the peritoneum, threaded with the two ends of the silkworm-gut ligature and withdrawn. The peritoneum and aponeurosis are then closed with continuous catgut sutures. The silkworm gut ligatures on the round ligaments are now pulled on until a short loop of the round ligament presents at the external abdominal ring, needles are threaded on each end of the ligatures and the loop of ligament on either side is sutured to the pillars of the ring so that when tied the pillars are approximated at the upper part of the ring, which is thus partially closed. The skin is then closed in the usual manner. Leicester has performed the operation in 20 cases with no unpleasant results but as yet has not had the opportunity of determining how it will stand the test of pregnancy.

Mercurochrome Ointment in Vaginitis.—The treatment of vulvovaginitis in children is certainly not standardized and perhaps it will be a long time before the profession will come to any agreement on this subject. A few years ago we called attention to the recommendation of Gellhorn that a 1 per cent silver nitrate ointment be used in these cases because he stated that he was getting superior results by the use of the preparation. DORNE and STEIN (*Ill. Med. Jour.*, 1924, 45, 219), who have been working on this problem for some time, have substituted a 1 per cent mercurochrome ointment for the silver nitrate, because it is less irritating, less astringent, and equally efficient as a germicide. The ointment is injected into the vagina by means of an ordinary irrigating glass syringe having a slender nozzle, to which a piece of soft rubber tubing 3 inches long and $\frac{1}{4}$ inch in diameter is attached. This tubing is introduced into the vagina and slowly pushed inward along the entire length of the vagina. The vagina is then slowly filled to capacity with the mercurochrome ointment, the excess of ointment being allowed to ooze back through the hymeneal opening, covering and protecting the irritated vulva. The tubing is changed for each patient and is sterilized by boiling. These treatments are given daily and no irrigations or other treatments are allowed, but a daily tub bath is insisted upon. The mothers are urged to change the children's underclothing frequently. The method is so simple that a large number of children can be treated in a short time and is painless so that the children coöperate readily. Since the cultural results were of no material assistance and in some cases failed to corroborate the smear reports, these investigators have ceased to make cultures and rely entirely upon smears in noting the progress of the case. Smears are taken at the beginning of treatment and are repeated every two weeks after a day of rest from treatment. When negative reports are obtained the smears are repeated at weekly intervals until three successive negative smears are obtained. Treatment is then suspended and a smear taken two weeks later and if

negative, repeated finally in three or four weeks to determine cure. Further observation is continued for a period equal to the time of the active treatment before the patient is discharged as cured. Furthermore, the cases are followed up for the next year to determine the permanency of the cure and to detect recurrence. As a result of their experience, Dorne and Stein state that vulvovaginitis in children can be cured by daily injections of 1 per cent mercurochrome ointment into the vagina. In gonorrheal cases they obtained a cure by this method in an average of 9.7 weeks, while in the non-gonorrheal cases cure was obtained in five weeks. In 20 cases which they were able to follow, there were no recurrences in the year following the treatment and therefore they urge the adoption of the method because of its many advantages.

Treatment of Benign Uterine Tumors.—In the Cleveland Clinic, CRILE (*Ill. Med. Jour.*, 1924, 45, 177) concludes with us that near, during or after the menopause, intramural fibroids of moderate size or fibrosis associated with hemorrhage should be treated by radium or radium plus deep roentgen-ray therapy. On the other hand, in the childbearing period he believes that operation should be advised because the mortality is less than 1 per cent (in his clinic) with permanent relief in nearly 100 per cent. Furthermore surgery assures the preservation of 100 per cent ovarian balance and preserves to a surprising degree the childbearing function. There is one type of operation which formerly baffled the surgeons but which Crile believes he has conquered, namely, the removal of a fibroid tumor from a pregnant uterus in which the growth is so situated that the obstetrician sees clearly that normal delivery cannot be made and that a premature abortion will destroy the fetus and to some extent imperil the mother. He has found in his experience that in cases where miscarriage attended operation, it did not occur during nor immediately after the operation, but usually twenty-four or more hours later—the miscarriage being preceded by a period of labor pains. In considering the large numbers of physical injuries unattended by fear that a woman may sustain without miscarriage, and on the other hand the frequency with which a miscarriage occurs as the result of a strong emotional shock, it occurred to Crile that the removal of the emotional factor might obviate the danger of miscarriage. He therefore adopted the following plan of treatment: (1) That the patient be kept in ignorance of the day appointed for operation; (2) that a physiological dose of morphin be given an hour before the administration of the anesthetic; (3) that the patient be given light nitrous-oxid-oxygen anesthesia in bed and be taken under this anesthesia to the operating-room; (4) that during the operation the entire field—abdominal and uterine—be blocked with novocain; (5) that during operation handling of tissues be reduced to a minimum; (6) that the patient be returned to her bed under anesthesia of light nitrous-oxid-oxygen; (7) that the patient be kept under morphin for forty-eight hours after operation, much water being given during this period; (8) that at the end of forty-eight hours the morphin be diminished, unless the slightest rhythmic pain occurs, in which case morphin should again be increased. By this plan of management he has removed myomata as large as the fetus and has even exposed the placenta without a single postoperative contraction pain. Another interesting group

of cases is the type of woman who is at or past the menopause, in whom examination reveals a normal vagina and cervix, no fibroid and but slight thickening of the uterine wall, the only sign of trouble being a slowly increasing amount of discharge which may or may not be stained with blood. Such patients as these belong in the precancer class, in fact, 5 or 10 per cent show cancer. Crile believes that a hysterectomy is indicated in such cases whether or not cancer is found, since if there is no cancer today, do we know that there will not be a cancer another day? Moreover, these senile changes are usually not cleared up by curettage. In brief, the patient secures safety against the future and relief from local trouble at the expense of but a trivial discomfort and a negligible risk.

Error to be Avoided in Ureteral Catheterization.—Some years ago it was decided to introduce as a routine procedure preliminary to roentgen-ray examination, shadowgraph catheters into the ureters rather than ordinary catheters when trying to determine the exact position of shadows suspicious of being in the ureter. In doing routine work, when a catheter is introduced into the ureter and is readily introduced some 25 to 35 cm., no evidence of obstruction or retention being encountered, one is naturally inclined to arrive at the conclusion that the catheter has reached the upper limit of the ureter and is resting somewhere near the kidney pelvis. Recently however, BEER (*Jour. Urol.*, 1924, 11, 425) had two such cases where the catheter entered readily and there was no suggestion that the catheter had turned on itself, but a roentgen-ray picture with the catheters in the ureter showed how faulty the inference was since in both instances the catheter twisted on itself a number of times and was lying in this twisted condition in the lower ureter, although the examiner might readily have inferred that it had readily passed to the kidney. It is apparent therefore, that unless one has a roentgen-ray control, one cannot infer, no matter how easily the catheters enter some 30 to 35 cm. up the ureter, that they are in fact in the kidney pelvis.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO; TORONTO, CANADA.

AND

DE WAYNE G. RICHEY, B.S., M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY, UNIVERSITY OF PITTSBURGH; PITTSBURGH, PA.

A Bacteriologic Study of Extirpated Tonsils.—Because of the important role played by the tonsils in focal infections, it is of interest to place on record the bacteriological findings in cultures made from the crypts of extirpated tonsils. JULIANELLE (*Jour. Lab. and Clin. Med.*, 1924, 9, 699) studied at the Philadelphia General Hospital a series of hypertrophied or septic tonsils from 147 patients, by culturing material removed from the depths of the crypts on the surface of beef-infusion blood agar. Further identification of the bacteria revealed that hemo-

lytic streptococci were encountered in 90.4 per cent; staphylococci in 62.5; Streptococci viridans in 31.2; *M. catarrhalis* in 19.7; *B. influenzae* in 17; pneumococcus in 8.8; *B. mucosus* in 5.4; *B. diphtheriae* in 4 and nonhemolytic streptococci in 1.3 per cent. In 8 instances pure cultures were obtained—hemolytic streptococci in 7 and Streptococci viridans in 1. The author indicates that the percentage incidence of the various bacteria in his work was somewhat lower than that of Pilot and his co-workers (*Jour. Inf. Dis.*, 1921, 29, pp. 47, 51, 55, 59 and 62), but was in fair agreement with that of Caylor and Dick (*Jour. Am. Med. Assn.*, 1922, 78, 570).

The Myocardial Lesions of Diphtheria.—After a most comprehensive résumé of the literature, WARTHIN (*Jour. Infec. Dis.*, 1924, 35, 32) found that the development of the theories of cardiac pathology in diphtheria presented an evolution closely paralleling that of the general theory and science of medicine during this period (1860–1924). The phases of this evolution, he classed as follows: “(1) Cardiac paralysis; (2) cardiac thrombosis; (3) infectious endocarditis; (4) endarteritis of cardiac vessels; (5) infectious parenchymatous myocarditis; (6) infectious interstitial myocarditis; (7) injury to cardiac nerves and ganglion, vagus, abdominal sympathetic and vasomotor system, resulting in cardiac paralysis; (8) toxic myocarditis; (9) special affinity of diphtheria toxin for the impulse-conducting system of heart (bundle of His).” In the attempt to clarify some of the questions and to give a more definite entity to the cardiac pathology of diphtheria, the autopsy material from 16 cases was studied grossly and microscopically. It was found that “the essential lesion of the heart in diphtheria was a toxic parenchymatous hyaline degeneration or necrosis, associated frequently with fatty degenerative infiltration and less frequently with cloudy swelling or simple necrosis.” If the patient survived a sufficient length of time a reparative inflammatory process (myocarditis), accompanied by muscle regeneration, followed the degenerative lesions. Either a complete regeneration or a fibrosis could result. Both the conducting and contractile mechanisms of the heart were damaged by the diphtheria toxin, there being no particular affinity for either apparatus. The author states that “the histologic picture in any given case will depend on the duration and stage of the infection, upon the degree of toxin injury to the muscle, the associated nutritional conditions, and the degree of muscle regeneration and accompanying fibrosis.” It was of interest that 9 of the 16 cases presented well-marked features of the thymicolymphatic constitution, “again an emphasis of the liability of this constitution to death from acute infections.”

Notice to Contributors.—All communications intended for insertion in the Original Department of this JOURNAL are received only *with the distinct understanding that they are contributed exclusively to this JOURNAL.*

Contributions from abroad written in a foreign language, if on examination they are found desirable for this JOURNAL, will be translated at its expense.

A limited number of reprints in pamphlet form, if desired, will be furnished to authors, *providing the request for them be written on the manuscript.*

All communications should be addressed to—

DR. JOHN H. MUSSER, JR., 262 S. 21st Street, Philadelphia, Pa., U. S. A.

THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

NOVEMBER, 1924

ORIGINAL ARTICLES.

ENDOCRINOLOGY FROM THE POINT OF VIEW OF THE
SURGEON.*

BY G. W. CRILE, M.D.,
CLEVELAND CLINIC, CLEVELAND.

THE surgeon sees the organs of internal secretion in three aspects: (1) When the incidence of some disease of the endocrine organs themselves, such as a malignant or benign growth or an infection, demands operative intervention; (2) when a hyperactivity of the gland is causing such destructive changes in the organism as to require the diminution of the secretion by partial extirpation; (3) when it is necessary to protect an organism stressed by the disease of some other part from the stimuli which may cause a hypersecretion of one or more of the endocrine organs. All of the endocrine organs, with the possible exception of the pineal, have this in common—that a hypersecretion may safely be corrected by the extirpation of a portion of the gland and that a hyposecretion may be compensated by the administration of the essential element in the secretion.

The first surgical removal of any of the endocrine organs—a thyroidectomy—was performed by Kocher in 1878, twenty-two years after Moritz Schiff had proved that the excision of the thyroid gland in dogs was invariably fatal. Kocher found that, although death did not follow complete extirpation of the gland in humans, a condition which he designated as “cachexia strumipriva” did follow. Following Kocher’s observations, Schiff continued his

* Read before Section N of the American Association for the Advancement of Science, Cincinnati, December 29, 1923.

observations on dogs, and found that the symptoms which followed complete extirpation of the gland could be prevented by thyroid therapy—a graft of the gland into some part of the body, injection of thyroid juice or the ingestion of thyroid gland.

Horsley, von Eiselsberg and others confirmed the observations of Kocher and the experimental findings of Schiff, and as a result Kocher soon modified his operation so as to leave *in situ* a portion of the gland. Just when the first removal of a portion of a gland in the treatment of hyperthyroidism was done I do not know, Kocher's original thyroidectomies having been performed for the removal of the unsightly huge tumors of such common occurrence in Switzerland. Partial thyroidectomy for hyperthyroidism, however, was an obvious and logical sequel of the experimental and clinical work of the men mentioned above, as has been the development of experimental and clinical studies of modifications of other organs of internal secretion.

It is not necessary to more than cite the association of certain investigators with these later studies. Thus, for example, Halsted is associated with the identification of the cause of tetany following parathyroidectomy; Halsted and Cushing with surgery of the pituitary body; Batty with the first removal of the ovaries for a general somatic condition; Dandy with the first operative approach to the pineal body; Cannon, Stewart and Rogoff, Hoskins and others with the effects of experimentally induced variations of adrenal activity; Marine, Kendall, the Mayos and others with experimental studies on the surgery of the thyroid gland. While the pancreas, spleen and, to some extent, the intestinal mucosa may be included among the endocrine organs, their surgical significance need not be considered in this connection. The thymus also is omitted from this discussion, since its activity may be controlled by radiation.

The modification of the symptoms of hyperthyroidism by partial thyroidectomy, and the reciprocal interrelation of such kinetic conditions as emotional stress, physical exertion, chronic infection or physical trauma, with the effects of increased thyroid secretion, and of increased adrenal secretion, led me some years ago to look upon a certain group of diseases which are almost invariably associated with excessive emotion or physical strain, infection, auto-intoxication, etc., as kinetic diseases, since in them there exists a diminished or an excessive activity of some one or more of these glands of internal secretion. Such conditions are nervous exhaustion, neurasthenia, hyperthyroidism, myxedema, adolescent goiter, cardiovascular disease, diabetes, Bright's disease, apoplexy, acute acidosis, thromboangiitis obliterans and certain cases of epilepsy. An attempt was made, therefore, to discover whether or not by lessening the activating secretions from the thyroid gland and the suprarenals some of these conditions might be controlled. Twenty-

four operations were performed, each of which included the division of one of the cervical sympathetics, adrenalectomy on the opposite side and partial thyroidectomy. In some, in addition, the other cervical sympathetic was excised. These operations include 13 for epilepsy, 4 for neurasthenia, 2 for diabetes, 3 for cardiovascular disease and 3 for thromboangiitis obliterans. Four cases of epilepsy showed very material improvement, and in certain other cases there was a temporary amelioration of symptoms, but, with the exception of one case of epilepsy, no permanent results have been achieved. In one case of apparently intractable diabetes there was a dramatic fall in the glycosuria on the day following the first operation, a fall which was maintained for a prolonged period, but as the patient was undergoing the Allen treatment at the same time the influence of the operation is debatable. In the control of the kinetic syndrome which we designate as hyperthyroidism, however, the role of the thyroid secretion is unquestionable, as is the role of partial thyroidectomy.

One peculiarity of each of the glands of internal secretion appears to be the power of influencing profoundly the entire organism, and many investigations have been undertaken for the purpose of identifying the specific manner in which the influence of each is manifested. Our own experimental investigations as to the nature of the special role played by the thyroid and the adrenals has led us to assign to these glands the title of *activators*, since we have found that adrenalin alone and thyroid secretion alone produce nearly all the symptoms produced by any cause of increased activation. Each causes increased metabolism; each causes increased activity of the other; each causes increased blood-pressure, increased pulse-rate, increased respiration, leukocytosis, sweating, dilation of the pupils, diversion of the blood to the surface, lowering of the threshold at the myoneural junction; each causes an early hyperchromatism of the brain cells followed by a chromatolysis if its administration is continued. When either is removed entirely the brain cells degenerate; the power to fabricate heat and mental action is progressively lost; after adrenalectomy death soon follows; after thyroidectomy life continues only in so far as it is expressed by a continued heart action; a sluggish circulation; an impersonal existence.

The fact that the essential content of the thyroid secretion is iodine and that iodine increases electric conductivity, together with our histological studies, led us to believe that the action of the secretions of these glands was electrical in character. In the course of certain biophysical researches, therefore, we found that in an iodized animal, whether iodized directly by the injection of iodoform or by feeding with thyroid extract, the electric conductivity of the brain was uniformly increased. In cases of protracted iodism, however, when the animal was in a state of exhaustion the

conductivity' was decreased. Identical changes in the conductivity of the brain followed the administration of adrenalin, a single injection being followed by an increase in the conductivity of the brain; repeated doses by a decreased conductivity of the brain. In each instance the liver showed changes in the opposite direction from those in the brain. That is, when the conductivity of the brain was increased during the stage of increased activation the conductivity of the liver was decreased, the opposite being true in the stage of exhaustion from either cause, that is, when the conductivity of the brain was decreased the conductivity of the liver was increased. These findings produce a powerful link in the chain connecting these two organs, not only with each other but with the brain and the liver.

In view of our histological findings in which, as stated above, the administration of either thyroid extract or of adrenalin was followed by an immediate hyperchromatism of the brain cells, with a later increased chromatolysis when the administration of either thyroid extract or adrenalin was continued, together with the corresponding changes in the electric conductivity and the findings in other experiments which link as irrevocably as these findings, the histological picture with the electric conductivity, we made an attempt to interpret the hyperthyroidism or hyperiodism, or adrenalism, in electrical terms. As further evidence to this end we made investigations to discover whether or not temperature changes were produced in the brain by adrenalin alone and by adrenalin in an iodized animal. We found that invariably the injection of adrenalin in the normal animal was followed by a characteristic increase in the temperature of the brain amounting to about 0.5°C. , the period of rise and fall being usually about ten minutes. In an iodized animal, on the other hand, the injection of adrenalin produced an abrupt rise in the temperature of the brain, in some instances amounting to from 1.5° to 2°C. , with as abrupt a return to below the normal temperature. Thus, again in these findings adrenalin and the essential element in the thyroid secretion prove their interrelationship and their essential effects upon the activity of the brain. It was significant that with the exception of the thyroid the temperature of no other organ or tissue was increased by the injection of adrenalin.

The effect of the normal adrenalin secretion upon the brain was dramatically shown by observing the temperature of the brain during asphyxia. As Cannon has shown, during asphyxia there is an increased output of epinephrin. During asphyxia the temperature of the brain shows the characteristic adrenalin curve. In a thyroidectomized animal the response of the brain to adrenalin was far less than in an animal with an intact thyroid.

Summary. The results of these studies, therefore, have provided fundamental evidence in favor of the theory that thyroid secretion

and epinephrin are essential elements in the operation of the electrochemical mechanism which we conceive the human organism to be; and that in the operation of the electrochemical mechanism the thyroid and the adrenals are indissolubly linked with the brain and the liver, their probable role being, as shown by these temperature studies, to control the oxidation within the brain whereby the electric charges which operate the mechanism are accumulated. The practical surgical bearing of these studies is that they point the way to an increased control of the factors which make or mar the surgical results.

If the oxidation which controls the activation of the brain is in turn controlled by the secretion of the thyroid and of the adrenals, then by so much as the activity of these secreting glands can be controlled by management, technic and environmental control, by so much will the hyperactivity of the brain be prevented and the organism conserved.

The proof that this assumption is correct is shown by mortality percentages and by morbidity results; since our efforts have been directed to the control of those factors which increase the activation of the organism, the mortality rate in the last 1000 thyroidectomies for hyperthyroidism has fallen to 0.8 per cent. In the last 720 bad-risk cases of hyperthyroidism it has been 1.2 per cent. Moreover, the same measures in acute abdominal risks of all kinds have reduced the mortality to 3.8 per cent. Our belief is that to the extent to which the activation of the organism can be depressed, to that extent will the organism be conserved.

THE DIAGNOSIS AND TREATMENT OF EXOPHTHALMIC GOITER (GRAVES' DISEASE).*

BY J. WILLIAM HINTON, M.D.,
NEW YORK.

(From the Goiter Clinic of Dr. Charles Gordon Heyd at the New York Post-Graduate Medical School and Hospital.)

A REVIEW of the cases of exophthalmic goiter (Graves' disease) admitted to the Goiter Clinic of the New York Post-Graduate Medical School and Hospital during the past two years, numbering 20, showed that the previous treatment consisted of:

1. *Physiological Rest, with Correction of Foci of Infection.* Two cases fell in this group. One had been under treatment for two

* I am greatly indebted to Dr. Heyd for the privilege of using the records of these cases in this review.

and a half years and 1 for one year. The patients were unable to work when seen.

2. *Roentgen-ray Therapy.* This group included 4 cases. They had had from four to ten roentgen-ray treatments. None of these patients were able to work.

3. *Radium Therapy.* Two cases were in this group. The first patient, who had had ten radium applications, was doing light work, but did not feel normal and his basal metabolism was 25+. The second patient showed a clinical picture of myxedema after eight applications, but did not return for the basal metabolism test. Follow-up letters were unsuccessful in getting the patient to return for treatment.

4. *Ligation of Superior Thyroid Arteries.** This series included 2 patients who had had their ligations performed five and six years previously. One patient was blind from corneal ulceration, and was 65 pounds under weight, after ligation of the superior thyroid arteries. The other was 50 pounds under weight, and was able to work only about eight months during the year after ligation of both superior and one inferior artery.

5. *Gynecological Treatment.* This group numbered 2. One had been operated on for displacement of the uterus, and three months later was operated for exophthalmic goiter. The other patient had had office treatment for uterine displacement for several weeks, and was operated upon one year later for Graves' disease. These cases gave an irregular menstrual history.

6. *Incomplete Surgery.* One case came under this heading. Four years before admission to Clinic the patient was operated upon, and had one lobe of the thyroid gland removed. The symptoms returned one year later, and the patient was then treated with injections of boiling water, without relief.

7. *By Ophthalmologist.* One case. This patient had a unilateral exophthalmos of several months' duration, and it was thought he had an intraorbital tumor. Roentgen-ray therapy was advised and given.

8. *By General Medical Treatment with Sedatives.* Six cases. These cases had been under medical care varying from three months to seven years. It is needless to say that these patients received only temporary improvement, or they would not have consulted a surgical clinic for their condition.

The Signs and Symptoms of Graves' Disease. The cardinal signs and symptoms of Graves' disease are: (1) Tachycardia; (2) tremor; (3) exophthalmos; (4) enlargement of the thyroid.

The secondary signs and symptoms are palpitation, insomnia, loss of weight, gastrointestinal disturbances, pigmentation and itching of skin, hyperhidrosis of hands and feet, disturbance of the

* The cases of this group, 1 of Group 5 and 1 of Group 8, are from my personal records.

menstrual function, flushed and warm feeling, emotional and irritable state.

The first positive findings are tachycardia and tremor. Tachycardia is a constant finding in these cases, and it is due to the selective action of the thyroxin on the accelerator nerves of the heart. The pulse does not become normal during rest in bed or while asleep. In the neglected cases there is an arrhythmia, which is a bad prognostic sign, as it indicates marked cardiac degeneration. Tremor is one of the earliest symptoms. The characteristic feature is its very fine type.

Exophthalmos is present in 85 per cent of the cases. It is not always present in the early stages of the disease, and may be unilateral in a small percentage of cases. Cases of several years' duration may give a history of intermittent exophthalmos. The exophthalmos seems to bear a direct relation to the cycles of thyrotoxicosis. It may entirely disappear during the interval between crises. It is due to the spasm of Landstrom's and Müller's muscles, both of which are innervated from the cervical sympathetic system. Dalrymple's sign is usually seen very early. This is a widening of the palpebral fissure. Von Graef's and Kocher's signs are present in the early cases. A lack of the upper lid to follow the globus oculi on looking down constitutes the former sign, and the same on looking up the latter sign. Stellwag's sign—a lack of winking, which is normally from three to five times per minute—is very variable and of little diagnostic value. Moebius' sign—lack of convergence of the eyes when looking at a fixed point—is also variable. Wood¹ states that dryness of the eyes is a common complaint in cases of Graves' disease. Dalrymple's and von Graefe's signs are due to spasm of Müller's muscle which runs from the superior palpebræ levator muscle to the tarsal cartilage.

The enlargement of the thyroid may not come on for a considerable period after other cardinal signs of Graves' disease, and is present in about 80 per cent of the cases. It is very variable, and may be present early or not until the disease is well developed. The enlargement is frequently intermittent and is directly related to the crises of the disease. At first there is a soft enlargement which becomes elastic as the disease progresses; in neglected cases it has a firm consistency. On palpation the thyroid gives a definite pulsation, and auscultation gives a bruit. This bruit has been described by Riesman,² and may be heard on auscultation over the eye. These cases, if neglected, undergo a fibrous tissue replacement and go over into the "burned-out thyroid" of Crotti,³ with a diminished secretion and, finally, myxedema.

The Secondary Signs and Symptoms of Graves' Disease. The most important is the loss of weight, which is very marked in the severe cases, and may amount to 40 or 50 pounds during the crisis of the disease. In the interval between the crises the weight may

become normal; some remain constantly under weight. One case in this series did not lose weight, but gained about 30 pounds during the first year of the disease.

The gastrointestinal disturbances are variable; a ravenous appetite is the rule in cases with marked loss of weight; anorexia is not uncommon. The case with marked gain in weight had anorexia. Diarrhea occurs occasionally in the severe cases, and is very annoying to the patient. Palpitation comes on in spells, and is quite frequently worse at night. It is a factor in causing insomnia. Insomnia is usually present in these cases, but they respond to almost any form of sedative.

The menstrual cycle in these cases is always irregular; the periods may be delayed and the flow very scant. In later cases amenorrhea may be present, this disturbance in the menstrual cycle being the reason for consulting the gynecologist. Loss of libido is also a frequent complaint. The heat production in these cases is greatly increased from the excessive protein destruction. The patients wear very few clothes in cold weather and are uncomfortable from heat in surroundings which the average individual finds comfortable.

Pigmentation of the skin is very frequently seen around the eyes and on the forearms. The skin may also be easily irritated by heavy clothing. Hyperidrosis of hands and feet is very annoying when present. The emotional and irritable state of these patients makes them very trying to live with.

The only laboratory data which have a definite place in the diagnosis and treatment of Graves' disease are the basal metabolism determinations. The basal metabolism is of value in diagnosing the early cases from colloid goiters with a psychoneurosis. In the former it is always elevated, but never in the latter condition. The basal metabolism has also a definite place in selecting the type of treatment to be employed, as well as in determining the prognosis. These cases go through cycles of thyrotoxicosis; and if the metabolism does not drop with conservative treatment the patient is in the ascending wave of the crisis, and any surgical procedure at this time is contraindicated. A metabolism of 60 or 65 + that will drop 10 to 15 points with rest in from seven to ten days gives a much better prognosis than a metabolism of a 40 +, which remains stationary during the same period. The Goetsch test is not usually employed in the diagnosis of Graves' disease at the present time, since it is liable to have a very deleterious effect on the patient, due to the action of adrenalin on the sympathetic nervous system, which is hypersensitive in this condition.

The urine analysis in these cases shows quite frequently a glycosuria. This is due to the fact that the pancreas and the thyroid have an inhibitory action over each other, and in hyperthyroidism the pancreas is inhibited to such an extent that carbohydrate metabolism is incomplete; likewise there is a hyperglycemia. The sugar

tolerance test is of neither diagnostic nor prognostic value. The differential blood count will show a diminution in the polymorphonuclear leukocytes and an increase in the number of lymphocytes. The number of leukocytes usually stays within normal limits. The diminution in the polymorphonuclear leukocytes is supposedly directly related to the severity of the toxemia.

The Clinical Tests. The blood-pressure is normal or diminished. This is due to the action of the thyroxin on the vasodilator fibers of the arteries. The Katzenstein test consists in taking the pulse and blood-pressure and then compressing both femoral arteries for one minute; if the heart has no myocardial degeneration the blood-pressure should rise and the pulse fall; the heart with slight degeneration will give a normal blood-pressure and pulse; in marked myocardial degeneration the blood-pressure drops and the pulse goes up. It is variable and of little prognostic value.

Treatment. The advice this group of patients had received depended entirely on the specialist seen, and each patient had been assured of relief by the method of treatment employed. Each patient had been definitely advised against surgery.

It is very important that these patients should be under the supervision of that group of men who afford the highest percentage of relief, namely, the surgeons. Falta and Meyers⁴ state that "roentgen-rays and radium usurp the field that was formerly accorded to purely medical treatment. For the time being, at least, the surgeon, as opposed to the radiologist, seems to have the better of the argument."

A very small percentage of these cases can be cured by medical treatment, but it is only in selected cases in which prolonged medical treatment promises satisfactory results, and with only those patients who can financially afford prolonged rest, without nervous tension, should this be undertaken. Roentgen-ray and radium have not given satisfactory results in the treatment of this condition. At present one cannot regulate the proper dosage, for too many or too few cells are killed, and the relief is either only temporary or the patient goes over into a state of diminished thyroid secretion with the clinical picture of myxedema, which is not an uncommon occurrence. In severe cases it should never be employed because thyrotoxicosis is quite frequently produced, with a fatality. Among the German surgeons the consensus of opinion is against the use of roentgen-ray in this condition. The serum from thyroid-ectomized sheep—Moebius' serum—has not given the results expected. The same can be said of the Rogers-Beebe thyroid residue.

So far, surgery offers the best means of restoring these patients to complete health, with the least financial loss and the lowest mortality rate. Surgery has given 80 to 85 per cent of cures in late cases, as against 20 per cent of cures by medical treatment.

These statistics are based on the fact that the surgical cases are usually taken from the ones that had not been improved by medical treatment and were turned over to the surgeon for relief.

Surgery should not be advocated in all cases when first seen. One may use conservative treatment for several weeks or several months before deciding to operate. The type of operation to be performed, whether ligation of the superior arteries or resection of the thyroid gland, will depend on the clinical picture, history and the basal metabolism rate. The preoperative treatment in these cases, with the selection of the proper surgical procedure in each case, is the main factor in reducing the mortality of this serious condition to about 1 per cent.

The preoperative routine used in this Clinic consists of repeated basal metabolism determination, with rest in bed; high carbohydrate diet, forced fluids; digitalis, mx, three times a day; luminal, gr. 1.5, every fourth hour; morphin, gr. 0.25, when necessary; Lugol's solution, m5, three times a day for ten days. Lugol's solution (Plummer) will change the type of secretion from that of Graves' disease to the form of a toxic adenoma, which is supposedly due to alteration in the formula of the thyroxin. This should not be employed longer than fourteen to twenty-one days. Following this procedure the metabolism will drop from 15 to 20 points in from seven to ten days in all cases not in the ascending wave of the disease. If they do not respond to the above routine they are in the crisis of the disease, and any surgical procedure is contra-indicated at the time, and should not be undertaken until there is a marked drop in the metabolism.

Graves' disease has been produced by Falta and Meyers⁵ experimentally in dogs and rabbits by the injection of thyroid extract, as well as by the extract of the struma removed in the operating-room. These animals have shown all the cardinal symptoms, as well as the histological picture of the disease.

The picture of Graves' disease has been produced in human beings by taking large doses of thyroid extract for the relief of obesity, with all the cardinal symptoms, including exophthalmos. This has subsided on discontinuing the medication, together with rest.

Crotti⁶ has expressed the opinion that Graves' disease is due to a thyronuropolyglandular condition, which is very true; but the thyroid gland is the chief factor at fault in the production of the condition, so the treatment should be directed at the thyroid gland instead of at the nervous system or at the other glands of internal secretion.

Conclusions. 1. Surgical treatment of Graves' disease has given a higher percentage of cures, with a lower mortality rate than the so-called conservative treatment.

2. Graves' disease has been produced experimentally in animals

from thyroid extract and the extract from the goiter removed at operation.

3. The review of this series would indicate a lack of coöperation by the various specialists in the treatment of this condition.

REFERENCES.

1. Wood, C. E.: The Ocular Signs and Symptoms of Exophthalmic Goiter, *Illinois Med. Jour.*, 1907, **11**, 263.
2. Falta and Meyers: *Endocrine Diseases*, 3d edition, P. Blakiston's Son & Co., Philadelphia, 1923, p. 73.
3. Crotti: *Thyroid and Thymus*, Lea & Febiger, Philadelphia, 1922, p. 415.
4. Falta and Meyers: *Endocrine Diseases*, 3d edition, P. Blakiston's Son & Co., Philadelphia, 1923, p. 154.
5. Falta and Meyers: *Endocrine Diseases*, 3d edition, P. Blakiston's Son & Co., Philadelphia, 1923, p. 71.
6. Crotti: *Thyroid and Thymus*, Lea & Febiger, Philadelphia, 1922, p. 465.

EVIDENCE THAT IDIOPATHIC EPILEPSY IS A SENSITIZATION DISEASE.

BY JOSEPH L. MILLER, M.D.,

CHICAGO.

RECENTLY Dr. Raulston and the writer made a report on the treatment of migraine by intravenous injections of a 5 per cent peptone solution. Evidence was presented at this time to support the view that migraine might belong to the sensitization group of diseases. Since the publication of this article the treatment has been employed in a considerable number of additional cases, with results that support our views expressed at that time—that such treatment has a distinct effect on the migraine seizures. The object of the present article is to call attention to the possibility that idiopathic epilepsy may fall in this same group.

Asthma, hay-fever, urticaria, a high percentage of eczemas and pruritus may be considered as due to sensitization or hypersensitiveness to protein. It is unnecessary to call attention to the varied clinical symptomatology in this group. They all have, however, several points in common, indicating the probable relationship of this group of diseases. Perhaps the most striking feature is their hereditary character, either the particular disease appears in the offspring or some other member of this group. Not infrequently one or more of these diseases appear in the same individual.

Nervous factors also play an important role in this group. This is especially marked in asthma, urticaria, migraine and epilepsy. Until comparatively recently asthma was considered a neurosis, and at present many physicians emphasize the importance of nervous influences. Urticaria and angioneurotic edema are clinically closely related. Foods that can be eaten with impunity may

excite an urticaria at periods when the patient is suffering from nervous strain. The importance of nervous factors in migraine or epileptic seizures is generally recognized. As a consequence of nerve strain the hypersensitiveness of the individual is apparently increased.

Migraine and epilepsy, like asthma, may first develop following some acute infection. Of the various acute infections thought to be responsible for the onset of epilepsy, scarlet fever is considered the most important. On the other hand, acute infections frequently exercise an inhibitory action on all this group. Asthma, which has proven resistant to all forms of therapeutics, including desensitization treatment, may temporarily disappear after a severe infection, as typhoid or pneumonia. No reference was found in the literature in regard to the effect of infections on hay-fever. Migraine very frequently will temporarily and sometimes permanently disappear after an acute infection, and this is also true of epilepsy. Tinel¹⁵ refers to the disappearance of epileptic seizures after typhoid and pneumonia. Spratling reported that epileptics who acquire tuberculosis frequently show amelioration or disappearance of seizures. Turnowsky¹¹ refers to 3 cases of established epilepsy, in all of whom the seizures subsided—2 after pneumonia and 1 after scarlatina. Hamilton¹⁰ reports 12 epileptics that acquired typhoid; 9 showed distinct improvement—1 of these was free from seizures after four years.

This improvement after infection might be explained on the basis of desensitization, as this is the accepted explanation in asthma.

Pregnancy not infrequently modifies asthma, migraine and epilepsy. All of these may subside temporarily during this period. On the other hand, they may first develop during pregnancy. Frank Coke²¹ recently refers to an asthmatic who was entirely relieved during six pregnancies. There are many other references in the literature to the favorable effects of pregnancy on asthma. Weir Mitchell²² reported that he had never seen epilepsy made worse by pregnancy—on the other hand, the seizures are often less frequent. Beraud¹⁶ observed the effect of pregnancy on 31 epileptics—8 were influenced unfavorably and 15 favorably. In 8 of these the seizures entirely disappeared during this period. As the placenta behaves as a foreign protein to the mother, it is possible that desensitization might result.

The above evidence is merely suggestive that migraine and epilepsy may be sensitization diseases. There is considerable therapeutic evidence to support this view. It has been reported especially by French physicians that after treatment for rabies, or after the use of diphtheria antitoxin, epileptic seizures have temporarily disappeared. Bouché and Hustin,²³ following this lead, treated a number of epileptics with normal horse serum with encouraging results.

Spangler's² use of snake venom in epilepsy, reported in 1908, in the light of recent developments deserves consideration. He was led to try this treatment after reading a report where a patient who had been subject to epileptic seizures for fifteen years had remained free for two years after being bitten by a rattlesnake. Snake venom contains both a poisonous peptone and a globulin. The peptone is largely a nerve poison; the globulin lessens blood coagulability and increases vessel permeability. As there was a theory at this time that the epileptic seizure was associated with increased blood coagulability, he ascribed his good results to modification of blood coagulation. His report on 36 cases treated by subcutaneous injections of crotalin showed that every patient was affected favorably, although in some instances the improvement was very slight, in others the seizures became infrequent, or the major attacks entirely disappeared. Three patients had been entirely free for two years or more and 2 for eighteen months. In some cases the seizures permanently disappeared after the first series of five to six injections. He advised, however, that after the first series the injections be continued at intervals of two to four weeks. This is strikingly in accord with our observations in the peptone treatment of migraine. Spangler's treatment appeared so irrational that no attempt was made in this country to verify his results. In France, however, reports have appeared from time to time recording the value of this treatment.

Held³ recently made a report on 400 cases of epilepsy treated with serum of animals previously injected with serum and spinal fluid from epileptics. He states that 18 per cent of his series had been free from seizures two to four years and only 30 per cent were not benefited. If there is any value in this treatment it is probably due to the effect of normal serum rather than to changes produced by previous treatment of the animals.

Lion,²⁴ in 1911, reported good results in epilepsy from injections of brain extract.

All of the above methods of treatment can properly be classed as protein therapy. Whether the results were due to non-specific desensitization or some other action of protein is a matter to be determined.

Recently two reports have been made by English physicians, which lend support to the above reports, or, at least, suggest that foreign protein injections can modify epilepsy. James Crockett¹² conducted a tuberculosis sanitarium where all patients received tuberculin. He observed that in case the patient, in addition, had epilepsy, the seizures usually disappeared. He then treated 23 cases of epilepsy with tuberculin injections, beginning with 0,000,000,01 cm., and gradually increasing the dose, never exceeding 0.4 cm., and always endeavoring to avoid a reaction. A total of eight to ten injections were given at approximately weekly intervals.

Eleven patients in this group, at the time the report was made, had been free from seizures for three months or more. One patient who had 309 major and minor seizures in the month preceding the treatment had been entirely free for nineteen months.

Almost simultaneously with this report there appeared in the *British Medical Journal* a brief article by Edgeworth.¹ He treated 20 epileptics with intravenous injections of a 5 per cent solution of peptone, beginning with 5 minims and gradually increasing to 20 minims. Nine of these patients had been at least temporarily benefited.

The above therapeutic evidence cannot safely be ignored. The question arises, What is the method of action of these various agents?

If we permit ourselves to assume that the epileptic seizure is an anaphylactic manifestation, it raises the question of possible non-specific desensitization. There appears in the literature an occasional reference to a specific food being responsible for the seizures. Others refer to the effect of diet upon the seizures. These isolated reports that food may play a role in the seizures are significant if not convincing. The most interesting investigation of this phase of the subject has been reported recently by Wallis and Nicol.¹⁷ They made protein skin tests on 122 insane epileptics; 46 of these gave positive reactions; 28 reacted to peptone, 15 to cereals, 15 to fish and meat, 9 to vegetables, 9 to eggs and 3 to milk. One hundred controls were tested in the same manner; 13 of these were normals, 70 dementia precox and 17 various other forms of insanity. Only 4 gave a positive reaction—all to peptone and all in patients with dementia precox. In case the test was made just previous to the seizure the patient might react to a number of proteins, although earlier he may have been sensitive to only one. Following a seizure all tests might become negative. This desensitization corresponds to the antianaphylactic state observed in animals after anaphylactic shock. On account of this period of desensitization they emphasize the importance of making the tests several days after a seizure.

In those sensitive to a particular food the withdrawal of this article from the diet was followed by striking improvement, the seizures entirely disappearing to return again in case the offending food was taken. This report furnishes the necessary evidence that in some cases of epilepsy food sensitization is responsible for the seizures. The objection might be raised that if food sensitization was an important etiological factor in epilepsy it would long ago have been recognized. It is well to recall, however, that only in recent years has asthma been considered a sensitization disease.

The work of van Leeuwen and Leydner⁴ furnishes some additional support to the sensitization theory, using a method first proposed by Freund for isolating a muscle-stimulating substance from the blood. They were unable to detect this substance in the blood of

normal individuals. They then attempted to isolate it from the blood of patients suffering from a variety of diseases. They found it present only in the blood of patients with asthma, urticaria, migraine and epilepsy. It is their opinion that this toxic substance is in some way related to their "allergic disposition." If these results are confirmed it would at least indicate a close relationship between this group of diseases.

There is considerable evidence that there is a non-specific desensitization. This subject was briefly discussed in our article on migraine. Longcope¹³ recently reviewed this subject. He states: "It seems impossible to avoid the conclusion that in animals sensitized to two proteins anaphylactic shock to one reduces temporarily the sensitiveness to the second." All admit that it is not as complete or as lasting as specific desensitization. Larson¹⁸ has recently reported he was unable to desensitize with peptone animals sensitive to egg albumen. This work, however, can scarcely be accepted as disproving non-specific desensitization. In addition to the laboratory experience on this subject there is considerable clinical evidence supporting the non-specific theory.

Frank and Strouse¹⁹ treated hay-fever patients with autogenous staphylococcus vaccines, and reported results that compare favorably with pollen therapy. Sutton, in a recent personal communication stated that during the past summer hay-fever patients who were not relieved by attempts at pollen desensitization obtained temporary relief after intravenous typhoid vaccine. These results are in accord with the observation of Rosenau and Anderson, that animals receiving repeated injections of foreign protein became highly insusceptible to anaphylactic shock. van Leeuwen and Varakamp⁷ report 2 patients relieved of hayfever following treatment with tuberculin. Rachmann⁵ has recently stated that he considers the treatment of asthma with bacterial vaccines as non-specific. Schottmüller⁸ reports 8 patients with bronchial asthma treated with intravenous non-specific vaccine; 7 of these were relieved of their asthma. It is safe to state that it has not been clearly demonstrated that autogenous vaccines are superior to stock preparations in treating the bacterial type of bronchial asthma. For several years we made it a routine practice to give all bacterial asthmas entering my service at Cook County Hospital two or three intravenous injections of typhoid vaccine. An occasional patient was promptly relieved. Those not benefited were treated with autogenous vaccine. In no case, however, that had failed to be relieved by the typhoid vaccine was there any benefit from autogenous vaccine.

van Leeuwen and Varakamp⁷ have recently reported on the use of tuberculin in asthma. They selected only those patients who gave a positive von Pirquet. It would be interesting to see, however, whether the result would not have been just as satisfactory

in those patients in which the test was negative. They used Koch's T.O.A. in doses, ranging from 1 cm. of a 1 to 100,000 solution, gradually increasing, but not exceeding 1 cm. of a 1 to 10,000 solution, and always endeavoring to avoid a reaction. If the dose was too large an asthmatic seizure was precipitated. Twenty-eight patients were included in their series. All gave negative or, at most, slightly positive protein skin tests, and were probably chiefly the bacterial type of bronchial asthma. They report 68 per cent completely relieved, 10 per cent greatly benefited, 18 per cent decidedly improved and 4 per cent not benefited. These results compare very favorably with those obtained by specific desensitization. Auld,⁶ following the suggestive animal experiments of Dale and Kellaway, demonstrating that peptone would prevent anaphylactic shock in guinea-pigs, undertook the treatment of asthma with intravenous peptone solution. All types of bronchial asthmas were included in his series. No actual figures were given in regard to the percentage relieved, but he reports he was highly pleased with the results. Patients with cat or dog asthma were relieved while still in contact with these animals.

The above clinical observations support the laboratory experimental work that desensitization is not strictly specific. This enables the physician to apply a therapeutic test in diseases where hypersensitiveness may be a factor. Recently a patient with a long-standing intermittent hydrarthrosis came under my observation through the courtesy of Drs. Plummer and Lewin. The precise periodicity of the seizures in many cases of this disease excited the suspicion that the trouble might be anaphylactic in character. This exact periodicity is occasionally observed in migraine. This particular patient developed his trouble every thirteen days. In reviewing the literature on this subject Bierring²⁰ reports that in 8 out of 9 patients with this trouble, who became pregnant, the seizures disappeared. This patient was first given peptone: As it excited a marked urticaria, typhoid vaccine intravenously was then used, the patient receiving about twelve injections. He has now been free from his trouble for eight months, although in his last report he states that he has recently had periodical stiffness of the knee, but no swelling, and has been advised to take a few more treatments.

My own experience in treating epilepsy by this method is too limited to be of value. Colleagues, however, have reported to me most satisfactory results both with peptone and tuberculin, confirming the work of Crockett and Edgeworth.

Summary. The clinical results reported in epilepsy should stimulate further investigation, both in regard to sensitizing agents and non-specific therapy, and it is the object of this presentation to create an interest in this subject. It is to be remembered that in recognized sensitization diseases, such as hay-fever, no one has

been able to secure anywhere near 100 per cent of cures. For this reason failures must be expected. It is also to be borne in mind that desensitization is not permanent—the treatment must be repeated at intervals in order to avoid recurrence.

BIBLIOGRAPHY.

1. Edgeworth, F. H.: *British Med. Jour.*, 1920, 2, 780.
2. Spangler, R. H.: *New York Med. Jour.*, 1912, 96, 520.
3. Held, W.: *Neurol. Centralbl.*, 1920, 39, 394.
4. van Leeuwen, W. S., and Leydner: *Brit. Jour. Exp. Path.*, 1922, 3, 282.
5. Rachmann, F. M., and Graham, L. B.: *Jour. Immunol.*, 1923, 8, 295.
6. Auld, A. G.: *Lancet*, 1923, 1, 790.
7. van Leeuwen, W. S., and Varakamp, H., *Lancet*, 1921, 1, 201-1366.
8. Schottmüller: *Deutsch. med. Wehnschr.*, 1922, 48, 1474.
9. Menninger, K. A.: *AM. JOUR. MED. SCI.*, 1921, 161, 884.
10. Hamilton, S. R.: *Jour. Am. Med. Assn.*, 1909, 53, 1906.
11. Turnowsky, W.: *Wien. klin. Wehnschr.*, 1901, 35, 1622.
12. Crockett, J.: *Brit. Med. Jour.*, 1921, 1, 458.
13. Longcope, W. T.: *Physiol. Rev.*, 1923, 3, 290.
14. Miller, J. L., and Raulston, B. O.: *Jour. Am. Med. Assn.*, 1923, 80, 1894.
15. Tinel, J.: *La médecine*, 1922, 3, 366.
16. Beraud: Quoted by Hamilton.
17. Wallis, R. L. M., and Nicol, W. D.: *Lancet*, 1923, 1, 741.
18. Larson, N. P., Haight, A. V. R., Alexander, H. L., and Paddock, R.: *Jour. Immunol.*, 1923, 8, 409.
19. Frank, I., and Strouse, S.: *Jour. Am. Med. Assn.*, 1916, 66, 712.
20. Biering, W.: *Jour. Am. Med. Assn.*, 1921, 77, 785.
21. Coke, F.: *British Med. Jour.*, 1921, 1, 372.
22. Mitchell, S. Weir: Quoted by Hamilton.
23. Bouché and Hustin: Quoted by Tinel.
24. Lion, M. D.: *Vrach. Gaz.*, 1910, 17, 1592.

SOME CARDIAC EFFECTS OF ATROPIN.

BY ROBERT DAWSON RUDOLF, M.D. (EDIN.), F.R.C.P. (LOND.),

AND

F. M. R. BULMER, M.B. (TOR.), B.Sc. (TOR.),

TORONTO.

(From the Department of Therapeutics, University of Toronto.)

EVERY medical man knows that atropin tends to hasten the heart's action, the pharmacological explanation being that it paralyzes the vagal nerve-endings in the heart, and thus allows that organ to run riot. The dose of the drug that is required to fully throw the vagus nerve out of action is at least $\frac{1}{50}$ gr., and in many people as much as $\frac{1}{3}$ gr. or even more is necessary.

The effects of many drugs vary not only in quantity but also in quality with the dose given, and atropin is a good example of the latter, in that the action of a small dose is the very opposite of that from a larger one. If a sufficiently small amount be administered

no hastening of the heart occurs, but rather a slowing, and it is with this slowing action that we are now concerned. Many books on pharmacology do not even mention this slowing, while a few do so in a casual way. Thus, A. A. Stevens¹ writes, "Prior to the acceleration (of the heart) there is occasionally some slowing from stimulation of the inhibitory center in the medulla, but this effect is always transient." But what we desire to show is that if the dose be sufficiently small this preliminary slowing is not transient, but lasts for many hours, and is the *only* effect of the drug on the heart-rate.

Petzetakis² demonstrated that there are two stages in the action of atropin on the vagus: (1) The one of vagal excitability, and (2) the one of vagal paralysis. In the first stage the heart tends to slow and a degree of heart-block may occur and extrasystoles appear; in the second stage the heart hastens and any block tends to lessen or disappear. With a large dose the first stage is transient and quickly followed by the second.

Until a couple of years ago our opinion of the action of atropin on the rate of the heart was the same as that of O. T. Osborne,³ who in his book says, "Atropin causes increased rapidity of the heart, raises the blood-pressure. The average dose is $\frac{1}{100}$ gr." After the work which is described below we now agree with V. E. Henderson,⁴ when he writes, "The normal therapeutic dose of atropin slows the heart centrally; the vagal endings are not paralyzed," and with H. McGuigan,⁵ when he says, "Small doses of atropin, if they influence the heart-rate, only slow it."

At that time one of us got several house physicians and senior students to try the drug in doses of $\frac{1}{100}$ gr. on patients and on themselves, and the results were either negative or else the heart was actually slowed. We thought that perhaps the drug was at fault, so tried the triturates of several makers, but always with the same results. When we used $\frac{1}{50}$ gr. or more the pulse hastened, and, by the way, the blood-pressure, both systolic and diastolic, tended to be lowered and never to be raised, most books to the contrary. We also noticed that even after large doses the heart was at first slowed, although it quickly then hastened, following exactly Petzetakis' two stages.

The matter seemed to be worthy of further and more systematic study, and during the past year we have tried the effects of small doses of atropin upon many healthy individuals and also on a certain number of abnormal people, nearly 100 people in all. The work was done in several stages.

1. Single doses of $\frac{1}{100}$ gr. were given hypodermically or by the mouth (the effects are the same by either route, but rather slower when the drug is given *per oram*). Nearly always the pulse-rate fell considerably and, further, stayed down for several hours. Fig. 1 shows this and also the lowered blood-pressure.

2. Next we tried the action in a different way. In some 50 individuals (many being medical students) the pulse was taken every hour or so for one day, in order to get the usual rate for the individual. Next morning $\frac{1}{100}$ gr. of atropin was given by the mouth, and the pulse counted in the same way. On the third day the rate was again taken. On the day on which the atropin was taken the average pulse-rate was nearly always lower, often by as much as 8 to 10 beats per minute. The average for the whole group was as follows: First day, -80.22; second day (atropin), -75.5; third day, -80.45.

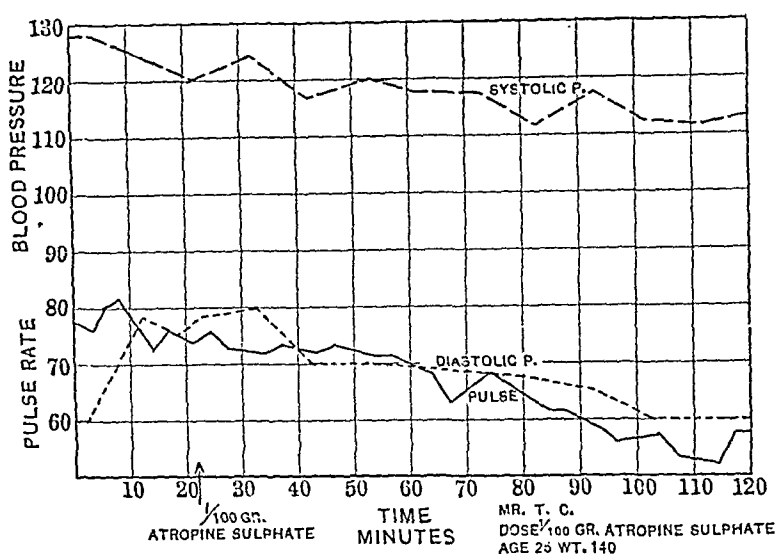


FIG. 1.—Slowing of pulse-rate and lowering of blood-pressure after $\frac{1}{100}$ gr. of atropin sulphate.

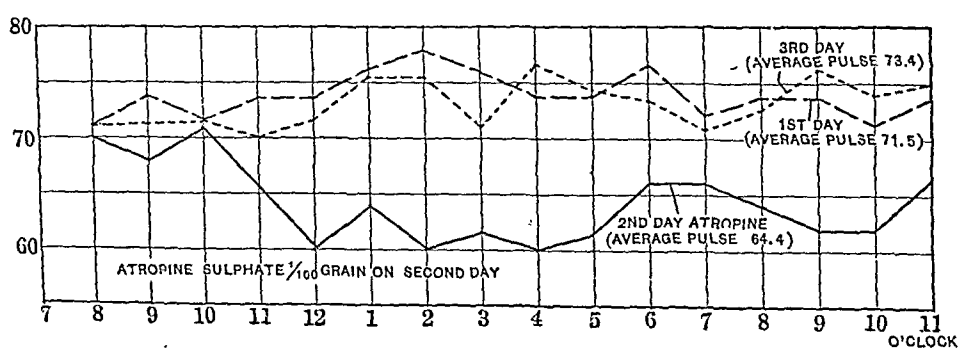


FIG. 2.—Pulse on three consecutive days. On second day $\frac{1}{100}$ gr. of atropin sulphate given and pulse slowed.

The slowing of the rate persisted for many hours, and often lasted all day after the dose given at 8 A.M. In a few instances there was little or no slowing or even a slight hastening. To such people a smaller dose was subsequently given, and in nearly every instance the heart was slowed. Evidently some people are more susceptible to the drug than are others. The average fall in our

series was not very great on account of these susceptible cases. Fig. 2 shows a typical finding.

The pulse on the atropin day was considerably lower than on the day before or the day after.

In another case (Fig. 3) $\frac{1}{50}$ gr. was given on the second day, and produced a preliminary slowing followed by a considerable rise which was succeeded by a prolonged slowing, as the dose in the blood diminished.

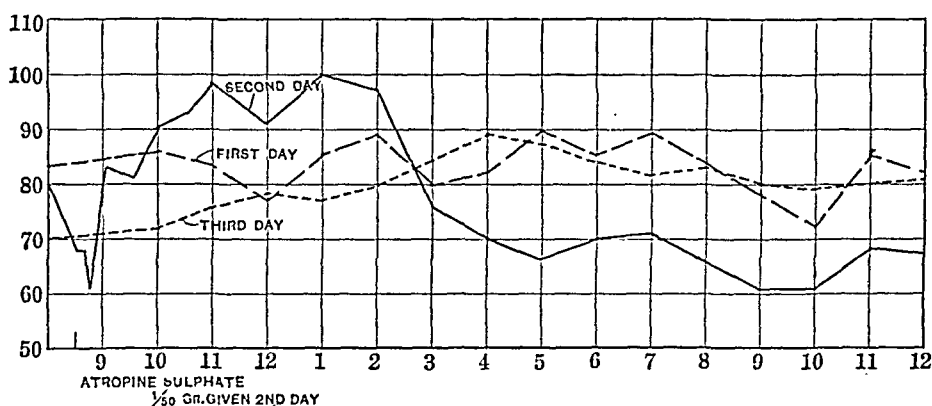


FIG. 3.—Atropin sulphate, $\frac{1}{50}$ gr., given by mouth. Preliminary slowing of heart, then hastening and final prolonged slowing.

3. If atropin in small doses increases the vagal excitability it should tend to enhance the effects of any other stimulation of the nerve.

Petzetakis found this to be the case in regard to ocular pressure. Pressure on the eye-balls tends to slow the heart reflexly through the vagus. If it be done in animals or in persons who have had preliminary small doses of atropin the effect is much more pronounced than usual. In the same way as digitalis somewhat slows the regular heart through the vagus, one would expect to see that when it is given in conjunction with small doses of atropin the slowing effect would be greater, and this we find to be the case. A number of individuals were put upon a dram of tincture of digitalis for a week, and it was found that the heart was very slightly slowed. Then a single dose of $\frac{1}{100}$ gr. of atropin sulphate was given, and the slowing became very much exaggerated, being in some instances as much as 40 beats per minute. Both the drugs were acting by stimulating the vagal centers. Fig. 4 shows such a case. The upper tracing gives the effects of atropin alone, the lower the effect of the same dose given after the individual had been on a daily dose of 1 dram of tincture of digitalis for a week. In this case when the pulse became very slow some degree of heart-block occurred. The amount of digitalis given would not likely of itself have produced any heart-block, but the combined effect of the two drugs did so. This fits in with J. T. Halsey's⁶ results,

where in dogs in which he had produced partial heart-block, by the use of digitalis or strophanthin, atropin in small doses increased the block.

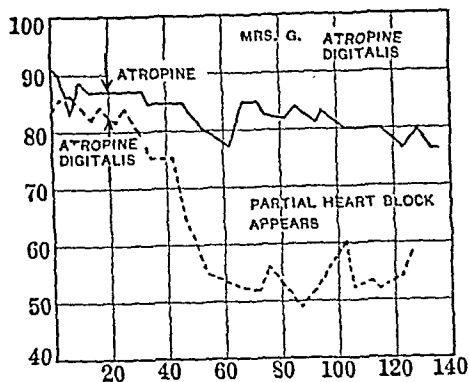


FIG. 4.—Digitalis and atropin. Upper tracing shows effect of atropin alone. Lower tracing, of atropin after a week of digitalis. Same individual.

4. If atropin in small doses increases heart-block due to digitalis, then one would expect to find that it would act similarly in block caused by other factors. We found this to be the case in several patients, of which the following is an example:

CASE HISTORY.—Miss A., aged twenty-eight years, had partial heart-block of unknown origin and of years' duration. Auricles were beating regularly at 60 per minute; ventricles irregular, run-

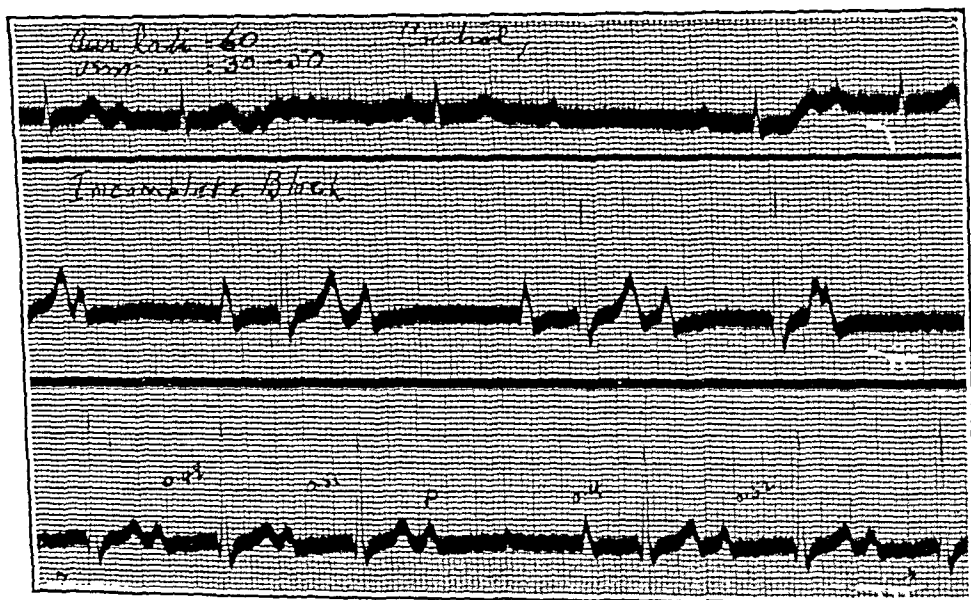


FIG. 5.—Partial heart-block.

ning at 30 to 50 per minute, due to occasional missed beats; P-R interval long, varying from 0.4 to 0.52 (Fig. 5). After exertion, such as from sitting up in bed, the pulse became regular and the

auricular and ventricular rates the same, but the P - R interval remained long (0.41 to 0.48). She was given $\frac{1}{50}$ gr. of atropin hypodermically. Five minutes later the block had increased, and the P - R interval was as much as 0.64. Thus, the first effect of the drug was to increase the block. Forty minutes after the atropin had been given the condition had changed, and now the auricles and ventricles were both beating at the rate of 70 per minute, and the P - R interval was reduced to 0.37. Thus, the first effect of the atropin was to increase the block by vagal activity, but this was soon followed by a decrease of the block as the vagal endings became paralyzed.

Next, this patient was put upon doses of $\frac{1}{200}$ gr. of atropin by mouth thrice daily. The block soon increased, and now *exercise did not remove it*. After seven days of this medication the block was so marked that every second ventricular systole was missed (Fig. 6). A few days after the drug had been stopped the condition was as before its administration.



FIG. 6.—Increase of heart-block in same patient as Fig. 5 after a course of small doses of atropin.

It is evident that if atropin be given in the treatment of partial heart-block the dose must be large or the block will be increased rather than diminished.

In a few cases of Graves' disease, in which we tried small doses of atropin, there seemed to be some slowing of the heart-rate, but one would need to test this in a large series of patients before being sure of this. It is interesting to remember that it has long been the practice of many clinicians to give belladonna in this disease,

and our findings would tend to support scientifically what has always seemed to be a purely empirical treatment.

Our work has chiefly been done in cases of regular heart, but, with the collaboration of Dr. Jamieson and Dr. Hepburn, we tried the effects of small doses of atropin in some cases of auricular fibrillation, some under the influence of digitalis and others without this. The ventricular rate was never lessened and usually hastened. This apparently paradoxical result can probably be explained as follows: Sir Thomas Lewis⁷ has shown that, while large doses of atropin by paralyzing the vagi cause increase in the refractory period, and in the duration of circuit movement with consequent lessening of auricular oscillations and often of ventricular systoles, stimulation of the vagi cause the opposite effect, with consequent hastening of the auricles and ventricles. Now, atropin in small doses stimulates the vagi, and hence may hasten the heart in the abnormal condition of auricular fibrillation. Hence, here it would be useless to use atropin as an adjuvant to digitalis. But it is otherwise in regular hearts and we have in atropin in small doses a drug that will slow such and which will enhance the effects of digitalis in such cases.

Summary. Atropin has two distinct effects upon the heart-rate when this is regular. In small doses it merely slows it, probably by stimulation of the vagal centers. In large doses, of course, it hastens it by paralyzing the vagal endings in the heart. It also then tends to remove any existing heart-block. If the dose be neither large nor small there will be no change in the heart-rate, the two effects of stimulation of the vagal centers and partial paralysis of the nerve-endings neutralizing each other. As already mentioned, individuals vary very much in their reaction to atropin. In most adults $\frac{1}{100}$ grain will merely slow the heart, in some no effect will occur while in a few a slight hastening sets in. In the last two groups it is usually only necessary to lessen the dose to get the slowing effect.

REFERENCES.

1. Stevens: Text-book of Therapeutics, 1923, p. 76.
2. Petzetakis: Presse méd., 1916, 24, 548.
3. Osborne: Principles of Therapeutics, 1923, p. 209.
4. Henderson: Jour. Pharm. and Exper. Therap., 1923, 21, 99.
5. McGuigan: Jour. Am. Med. Assn., 1921, 76, 338.
6. Halsey: Jour. Exper. Med., 1917, 25, 729.
7. Lewis: Heart, 1921-1922, 9, 241.

THE MYOCARDIUM IN NON-INFECTIOUS MYOCARDIAL FAILURE.*

By B. J. CLAWSON, M.D.,
MINNEAPOLIS.

(From the Department of Pathology, University of Minnesota.)

WHEN symptoms of chronic myocardial failure are present many clinicians make a diagnosis of chronic myocarditis, without regard to the pathological type of heart disease that may be present. Others use the term chronic myocarditis in a narrower sense to include only idiopathic hypertrophy with myocardial failure (hyperpiesia).

In chronic myocardial failure patches of fibrous tissue of varying distribution and size are frequently found in the myocardium and, according to one view, these are inflammatory in origin. Aschoff and Tawara¹ and Coombs² consider that some fibrosis may result from acute rheumatic fever. Brooks³ finds fibrosis in a high percentage of cases of endocarditis. According to another view, the fibrosis for the most part is not infectious in origin and, to express the idea, such terms are used as senile heart, the arteriosclerotic heart, cardiosclerosis, etc.

The purpose of this paper is to determine the extent and character of the anatomical changes in the myocardium in chronic myocardial failure and to find the cause of these changes.

Material. A detailed gross and microscopical study was made of the myocardium in 102 hearts which had been preserved and were available for study. The coronaries were carefully traced to determine the extent of the thickening of their walls and the narrowing of their lumina. The degree of coronary sclerosis is expressed in grades of 1 to 4. A grade 1 signifies just enough thickening to be noticed, and grade 4 signifies a condition where the coronaries are practically closed in one or more places. Degrees 2 and 3 are intermediate. Degrees 1 and 2 are referred to as slight and 3 and 4 as serious. The condition of the orifices was especially noted. This is particularly important in cases with syphilitic aortitis. The orifices are never seriously involved in arteriosclerosis of the senile type. Both gross and microscopical search was made for thrombi in the coronaries in various parts of the heart wall. The myocardium of both right and left ventricles was dissected for the gross determination of fibrotic areas. Microscopical sections were studied from five different areas: From both apices, from the middle part of both ventricles and from the septum. A careful

* The term non-infectious includes conditions not immediately associated with an acute infectious or toxic process.

search was made for fibrotic areas and inflammatory processes, such as exudates and Aschoff nodules.

Conditions in which Non-infectious Myocardial Failure May Occur. For convenience the 102 cases of myocardial failure have been separated as follows: Group I, cases of hyperpiesia that died of myocardial failure, 37 cases. Group II, cases of hyperpiesia with slight cardiac decompensation that died of cerebral hemorrhage, 7 cases. Group III, cases of chronic glomerulonephritis with cardiac decompensation, 3 cases. (Twenty other cases of chronic glomerulonephritis without cardiac failure, not included in the series of 102 hearts, have also been studied for comparative purposes in respect to the presence of myocardial fibrosis.) Group IV, cases of myocardial failure with right ventricular hypertrophy and dilatation resulting from increased intrapulmonary resistance, 4 cases. Group V, cases of sudden death associated with coronary sclerosis without previous symptoms of cardiac decompensation, 19 cases; in 6 of these thrombi were found in the coronaries; from the size of the hearts it is evident that a hypertension had been present in all of these except 3. (Groups I to V inclusive may be considered for the most part hypertensive hearts.) Group VI, hearts with hypertrophy from healed valvular defects, 21 cases. Group VII, hearts with luetic aortitis with involvement of the aortic ring (aortic insufficiency), 9 cases. Group VIII, cases with cardiac failure following hypertrophy due to an adherent pericardium, 2 cases.

Frequency. Non-infectious myocardial failure occurred 202 times (12 per cent) in a series of 1682 adult necropsies performed at the University of Minnesota during the years 1920-1923. Approximately two-thirds of these 202 hearts are hypertensive (hyperpiesia, glomerulonephritis and right ventricular hypertrophy) types. The remainder are cases of valvular defects, syphilitic aortic insufficiency and adherent pericardium.

Structural Changes in the Myocardium. The anatomical conditions which may be considered as causes of myocardial failure are: (1) Coronary sclerosis; (2) an inflammatory process; (3) fibrosis (atrophy of the fibers with replacement by connective tissue).

Coronary sclerosis was found in minor degrees in 44, and in serious degrees in 23 of the 102 hearts (Table I). Of the 23 with serious coronary disease 6 were in Group I, 1 in Group II and 19 in Group V. Severe coronary sclerosis occurs only in these three groups. Minor degrees of coronary sclerosis are common in advanced life and seem to be independent of other diseases. In 35 hearts the coronary arteries were normal.

Evidences of a slight degree of *chronic inflammation* are present in 10 of the 102 hearts—in 1 with right ventricular hypertrophy, in 7 with valvular defects, in 1 with syphilitic aortitis and in 1 with adherent pericardium (Table II).

In 50 of the 102 hearts no *myocardial fibrosis* was found (Table

TABLE I.—CORONARY SCLEROSIS.

Group.	No. of cases.	Grades.				Absent.	Present.
		1.	2.	3.	4.		
I	37	19	6	5	1	6	31
II	7	1	2	0	1	3	4
III	3	0	0	0	0	3	0
IV	4	0	0	0	0	4	0
V	19	0	0	13	6	0	19
VI	21	7	3	0	0	11	10
VII	9	2	0	0	0	7	2
VIII	2	1	0	0	0	1	1
Total	102	30	14	15	8	35	67

TABLE II.—EVIDENCES OF CHRONIC INFLAMMATION.

Group.	No. of cases.	Chronic myocarditis.			Aschoff nodules.			Absent.	Present.
		R.-L.	R.	L.	R.-L.	R.	L.		
I	37	0	0	0	0	0	0	37	0
II	7	0	0	0	0	0	0	7	0
III	3	0	0	0	0	0	0	3	0
IV	4	1	0	0	0	1	0	3	1
V	19	0	0	0	0	0	0	19	0
VI	21	1	1	1	1	2	4	14	7
VII	9	1	0	0	0	0	0	8	1
VIII	2	0	0	0	0	0	1	0	1

TABLE III.—MYOCARDIAL FIBROSIS.

Group.	No. of cases.	Gross fibrosis.			Microscopical fibrosis.			Marked.	Moderate.	Slight.	Absent.	Present.
		R.-L.	R.	L.	R.-L.	R.	L.					
I	37	0	0	11	14	0	6	1	6	13	17	20
II	7	0	0	0	0	0	2	1	1	0	5	2
III	3	0	0	0	0	0	0	0	0	0	3	0
IV	4	0	0	0	1	0	0	0	0	1	3	1
V	19	0	0	10	13	0	4	5	7	5	2	17
VI	21	0	0	5	7	0	0	0	0	7	14	7
VII	9	0	0	0	3	0	0	0	0	3	6	3
VIII	2	0	0	1	2	0	0	0	0	2	0	2
Total	102	0	0	27	40	0	12	7	14	31	50	52

III). In 31 it was present in only a slight degree and therefore cannot be considered as a cause of myocardial failure. In the 21 remaining hearts fibrosis was present in moderate or severe degrees, and may have contributed to the failure of the muscle. These 21 cases are all in Groups I, II and V. in hearts in which coronary sclerosis is conspicuous.

Relation of Myocardial Fibrosis to Coronary Sclerosis (Tables I and III). In the 37 hearts of Group I myocardial fibrosis was found in 20, in 19 in association with coronary sclerosis and in 1 in the absence of coronary disease. The distribution of the areas of fibrosis corresponds to that of the diseased arteries. All hearts with serious coronary sclerosis show some myocardial fibrosis.

In the 7 cases of Group II coronary sclerosis was found in 4 hearts, in 2 of which myocardial fibrosis also occurred.

In the hearts of Group III there is neither coronary sclerosis nor myocardial fibrosis.

In Group IV, with right ventricular hypertrophy, no coronary sclerosis is found. Myocardial fibrosis is present in 1. This heart is from a girl, aged eighteen years. The degree of fibrosis is slight, and Aschoff nodules are found. In this case the fibrosis is evidently rheumatic in origin.

In the 19 hearts in Group V coronary sclerosis occurs in all, and myocardial fibrosis is present in 17. In all of the hearts coronary sclerosis is of a severe degree, and the amount of myocardial fibrosis is usually correspondingly extensive.

Minor degrees of coronary sclerosis were found in 10 in the 21 hearts of Group VI, in which failure was due to healed defective valves. Myocardial fibrosis is present in a slight degree in 7 of these 21 hearts. It occurs only in 1 where there is no coronary sclerosis. In this group coronary sclerosis, although of slight degree, may be a factor in causing myocardial fibrosis, but there is another more probable cause, since Aschoff nodules are present in 7, indicating a previous rheumatic infection, which may also give rise to slight fibrosis.

In the 9 hearts of Group VII, in which myocardial failure followed syphilitic aortitis, coronary sclerosis is present in 2, and in both of these cases myocardial fibrosis is present to a slight extent. In 1 the fibrosis is associated with a chronic inflammation, probably syphilitic in origin. In the other the fibrosis probably followed coronary sclerosis.

One of the 2 hypertrophied hearts with adherent pericardium shows slight coronary sclerosis. Both show myocardial fibrosis, but in the one with the normal coronaries Aschoff nodules are present.

The relation of myocardial fibrosis to coronary sclerosis is obvious, especially in Groups I, II and V, in which there has not been a previous infectious process. It appears highly probable that coronary sclerosis causes all myocardial fibrosis, except a few of slight

extent due to rheumatic infection and rare instances of myocardial lues.

Relation of Myocardial Fibrosis to Rheumatic Infections (Table II). That a fibrosis of the myocardium, periarterial in character, may follow rheumatic infections has been shown by Beattie and Dickson⁴ and others. The presence of Aschoff nodules as an indication of a rheumatic infection has been established. These tend to disappear after an acute attack, but they may remain for years. It is generally believed that rheumatic infections are responsible for about 85 to 90 per cent of healed valvular defects, and that in practically all cases of valvulitis there is a myocardial involvement.

In none of the hypertensive hearts is there any indication of a rheumatic myocardial involvement, shown by the presence of the Aschoff nodules, except in 1. This is the heart of a girl, aged eighteen years, which failed from increased intrapulmonary resistance. Neither is there any indication of a previous rheumatic infection in the 9 hearts with aortic insufficiency associated with syphilitic aortitis. In the 7 cases with valvular defects in which myocardial fibrosis is present it is probably due to a rheumatic infection, since the Aschoff nodules are found. The fact that a non-tuberculous pericarditis is frequently rheumatic in origin would suggest that the fibrosis found in the hearts with an adherent pericardium was produced by a rheumatic infection.

It is seen that there is evidence of a rheumatic origin of myocardial fibrosis in only 10 of the 52 cases. In general, it may be said that rheumatic fibrosis is always of slight degree, and that in most instances myocardial fibrosis is not rheumatic in origin. As far as these observations go, an extensive myocardial fibrosis is never rheumatic.

Relation of Myocardial Fibrosis to Lues (Table III). Warthin⁵ is apparently of the opinion that myocardial fibrosis is usually due to syphilis. He states that the fibroid heart is the ultimate outcome of all latent syphilis. In his material he found that coronary sclerosis might or might not be associated with syphilitic myocarditis. He found marked coronary sclerosis to be a rather rare association. Even in the 9 cases of definite syphilitic aortitis in our series there were only 3 instances of myocardial fibrosis, and 2 of these seemed to be due to coronary sclerosis of the ordinary type. Lues of the myocardium appears to be rare.

Relation of Myocardial Fibrosis to Strain. The various kinds of strain which may result in hypertrophy and dilatation of the heart are: (1) Increased systemic arterial resistance, as in essential hypertension and chronic glomerulonephritis; (2) increased pulmonary resistance, as is found in bronchial asthma and pulmonary emphysema; (3) strain, non-hypertensive in character, as that found with valvular defects, syphilitic aortic insufficiency and adherent pericardium.

In the hyperpiesia hearts (Groups I and II) myocardial fibrosis occurs in 14 in both ventricles and in 8 in the left ventricle alone. It is true that there is strain on the right ventricle after decompensation begins, but the chief strain is on the left ventricle, and one would expect much more pronounced changes on the left side if hypertensive strain causes fibrosis. The 22 hearts without fibrosis in Groups I and II average 565 gm. in weight. Judged by their weight these hearts were subjected to as high a degree of hypertension as those with fibrosis.

In the 3 cases of chronic glomerulonephritis with myocardial failure there was no fibrosis. In 20 other cases of chronic glomerulonephritis, with hearts ranging in weight from 500 to 760 gm., there was no fibrosis except in 1, aged sixty-nine years; with coronary sclerosis. The persons with chronic glomerulonephritis are in general much younger than those with myocardial fibrosis.

There is no fibrosis in the cases of right ventricular hypertrophy, except in 1 which had associated Aschoff nodules.

It is apparent therefore that there is no evidence to support the view that hypertensive strain causes myocardial fibrosis. Fibrosis is absent in cases of hypertension that do not have coronary sclerosis. This agrees with Allbutt's⁶ statement that in hyperpiesia hearts the myocardium is usually normal microscopically.

Judged by the extent of the ventricular hypertrophy there is often a severe strain on the myocardium in hearts with valvular defects. If such strain is a cause of myocardial fibrosis, as believed by Stadler,⁷ these hearts should show this change. In the 21 hearts with valvular defects myocardial fibrosis of a slight degree was found in 7, and in all of these Aschoff nodules were found, indicating that the fibrosis was inflammatory in origin. In the 14 cases without fibrosis the average weight was 550 gm., indicating long-continued myocardial strain. In 1 case, a man, aged forty-four years, with aortic stenosis, the heart weighed 1130 gm., but no fibrosis was found.

In the 9 cases of luetic aortic insufficiency a slight fibrosis was found on microscopical examination in 3. In 1 of these there were many lymphocytes and the appearance suggested lues. There is often some narrowing of the coronary orifices in this disease. There is no evidence here that strain causes fibrosis.

In 1 of the cases of adherent pericardium the slight myocardial fibrosis may be explained on a rheumatic basis, in the other with a gross fibrosis the cause is not clear. It may be due to coronary disease or to a rheumatic infection.

There is no satisfactory evidence that strain of the non-hypertensive type ever causes myocardial fibrosis.

Conclusions. The anatomical changes in the myocardium have been studied in myocardial failure resulting from hyperpiesia,

chronic glomerulonephritis, right ventricular hypertrophy, defective valves, luetic aortitis and adherent pericardium.

There are no anatomical changes except coronary sclerosis and myocardial fibrosis.

Coronary sclerosis of serious degree was present in 22.5 per cent.

Myocardial fibrosis was found in a marked or moderate degree in 20.5 per cent and in a slight degree in 30 per cent.

There is usually a close correspondence between the situation and extent of myocardial fibrosis and the distribution and degree of the coronary sclerosis.

Myocardial fibrosis is usually due to coronary disease, but occasionally rheumatic infections may give rise to a slight degree of fibrosis.

Myocardial strain (hypertensive or non-hypertensive) is not a cause of myocardial fibrosis.

Luetic myocarditis is rare.

Myocardial failure is rarely due to anatomical changes in the myocardium. It may be explained as an exhaustion of the cardiac muscle.

True chronic inflammation of the myocardium is very rare. What is commonly called "chronic myocarditis" is usually myocardial fatigue resulting from the various conditions mentioned above.

Approximately half of the cases of myocardial failure show no anatomical changes in the heart muscle.

The anatomical changes in the heart muscle are seldom sufficient in themselves to cause death.

BIBLIOGRAPHY.

1. Aschoff and Tawara: Brit. Med. Jour., 1906, 2, 1103.
2. Coombs: Quart. Jour. Med., 1909, 2, 26.
3. Brooks, H.: AM. JOUR. MED. SCI., 1911, 142, 781.
4. Beattie and Dickson: Textbook of Special Pathology, 1921, 2, 529.
5. Warthin, A. E.: Am. Jour. Syphilis, 1918, 2, 425.
6. Allbutt, C.: Diseases of the Arteries, 1915, 2, 8.
7. Stadler: Deutsch. Arch. f. klin. Med., 1907, 91, 98.

A STUDY OF FOUR THOUSAND REPORTED CASES OF ANEURYSM OF THE THORACIC AORTA.

BY LINN J. BOYD, M.D.,

ANN ARBOR, MICH.

THE fact that there are over 5000 cases of thoracic aneurysm reported in the literature shows the subject is regarded as one of importance and interest. A majority of the papers consist of case

reports with a comment upon some unexpected feature, not rarely an unforeseen postmortem diagnosis. It was thought advisable to undertake a review of the subject in order to ascertain, if possible, the reasons for continuing to make mistakes and to suggest remedies. In this paper, no statistical report previously made will be included unless the report was based upon personal observation. No theories will be advanced to explain the numerical results of the survey since the aim of the report is to make a statement of fact rather than engage in the polemical aspects of the problem.

Incidence. Thoracic aneurysm is not rare. It probably represents the cause of mortality in 0.1 to 0.5 per cent of deaths in American cities. In postmortem statistics, it is found in a variety of figures varying from 0.1 to 0.9 per cent; 0.3 per cent being about the average. More instructive is the relationship between the reports of: (1) Out-patient dispensary services and (2) hospital in cases. The diagnosis is made nearly fifteen times as often in the latter group. This disparity cannot be accounted for upon the basis of a difference in the degree of symptoms except in the minority of cases. It can be explained by assuming a difference in the degree of minuteness of the examination given in the two services.

Predisposing Causes. **SEX.** Aneurysm of the thoracic aorta is 5.6 times as common in males as in females. All statistics give males a marked predominance although the figures vary from 10 to 3 up to 11 to 1.

FEMALE  606

MALE  3403

CHART I.

AGE. Aneurysm may be seen at any age. It has been reported in the infant and in the very aged. The curve of incidence rises slowly from birth and reaches a maximum in the period from thirty-six to forty years and then falls more slowly. While aneurysm is usually discovered in the years of greatest physical activity, it must be considered as a diagnostic possibility at any age. In 3690 cases, the exact age was stated and 2791 or about 75 per cent were between the ages of thirty and sixty.

AGE INCIDENCE IN MALES. The curve of incidence in males rises slowly from birth until the twenty-fifth year and then rapidly reaches a maximum in the thirty-six to forty-year period. The curve of descent is more gradual. The course of the curve confirms the universally accepted dictum that the maximum frequency of aneurysm corresponds to the period of greatest incidence of syphilitic vascular disease.

AGE INCIDENCE IN FEMALES. The largest number of cases in females is found in the forty-six to fifty-year period, ten years later

than the maximum for males. Up to the forty-one to forty-five-year period, the curves are similar but in the next five years instead

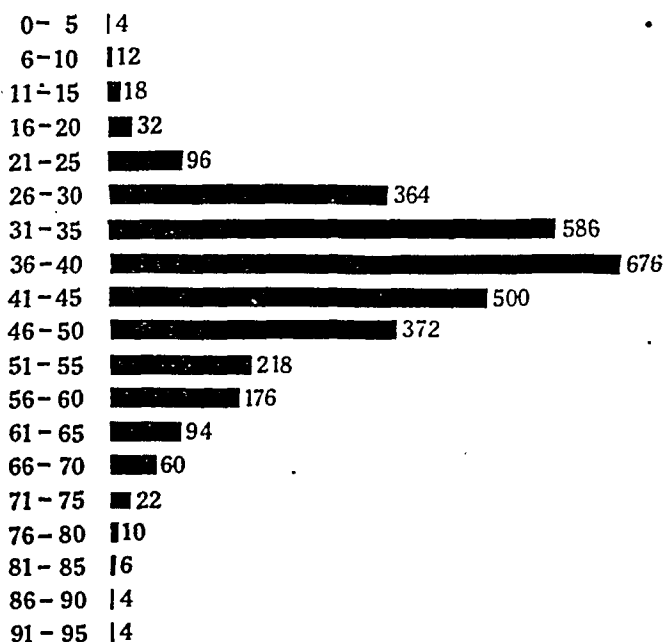


CHART II.

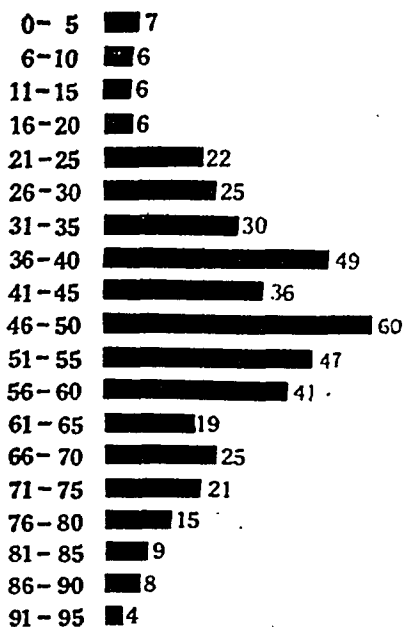


CHART III.

of the expected fall, there is a rise. From this age until sixty-five there is a steady fall and then the third apex. At seventy-five, the number of cases for both sexes is equal. Owing to the fact that, in

only 436 female cases the exact age was stated, it is inadvisable to draw conclusions as to the significance of the various peaks. The first two apices seem to correspond to the two ages of syphilitic infection. The third is not solely arteriosclerotic since there is no similar apex in the male.

RACE AND OCCUPATION. The colored race is notoriously liable to aneurysm probably due to the increased incidence of syphilis in that race. The role of occupation has been stressed by many writers. Sudden violent exertion in adults precipitates many latent aneurysms but probably does not cause them. The writer recently observed a syphilitic male, aged thirty-four years, who was under treatment for syphilitic aortitis. His occupation of a truck driver necessitated heavy manual labor. Sometime ago while cranking a machine, the engine back fired, the crank striking the man in the chest. Since that time, the man has complained of the symptoms and has given the physical signs of aneurysm of the ascending aorta. Had not the writer had knowledge of the patients' syphilitic aortitis, he might have been inclined, as many others have been, that the etiology was strain or trauma. It is probable that the association of syphilis, alcohol and hard work in the same type of individual is more important than occupation itself, although there has been a sufficient number of aneurysms found in non-syphilitic children (usually suffering from whooping-cough) to warrant the view that stress and strain play more than a minor part in some cases.

Determining Causes. INFECTION. A very great majority of the cases are due to infection, syphilis standing out beyond any other. Estimates vary from 25 per cent (Klemoerer) up to 92 per cent (Rasch). Instead of citing proof of this point from the pathological standpoint, it was thought more interesting to note the time interval between the infection and the production of the first symptoms of aneurysm. This was noted in 200 cases and it was found that the average time was twenty years, which corresponds in general to the upper limit of the maximum of time interval for syphilitic aortitis. The minimum time was one year (syphilitic aortitis has been reported within six months). The upper limit was fifty-six years after infection. In 1 case a beginning aneurysm was found at autopsy when the chancre was still upon the penis. The possibility of coincidence is too great to include this case. The importance of these figures outside of showing the usual time interval is to emphasize that the syphilitic individual remains throughout his life potentially aneurysmal. Of the other infections, the septicemias are at times the cause of mycotic embolic aneurysms, while other infections may pave the way for an arteriosclerotic process.

HYPERTENSION. Prolonged hypertension plays a part in the production of arterial degeneration. Much more important in the production of aneurysm is sudden increased intravascular tension resulting from sudden violent physical exertion.

Location of the Lesion. The ratio of aneurysms in the various portions of the aorta is approximately 10-7-3-1. This has an important relationship to the symptoms.

ASCENDING	████████████████████	1675
ARCH	██████████████████	1106
DESCENDING	██████████	506
THORACIC	██	156

CHART IV.

1. **ANEURYSM OF THE ASCENDING AORTA.** Aneurysm of the ascending aorta has been divided into two types: (1) Of the intra-pericardial portion (aneurysm of symptoms) and (2) of the extra pericardial portion (aneurysm of physical signs). In reference to the first type, it should be noted that they are usually found at the sinus of Valsalva upon the right anterior surface of the aorta. These aneurysms of symptoms are prone to rupture before manifesting marked physical signs unless aortic regurgitation complicates. The symptoms are those of syphilitic aortitis. Since the second type has large sacs which displace and compress neighboring structures, they have been denominated "the aneurysm of physical signs."

2. **ANEURYSM OF THE ARCH.** This is another aneurysm of symptoms. They are usually found upon the posterior or posterior inferior part of the vessel and tend to involve the orifice of the innominate artery. The usual growth is backward so that the various vital structures in the vicinity of the dorsal surface suffer early. Anterior growth causing midline tumor is known but is not as common.

3. **ANEURYSM OF THE UPPER DESCENDING AORTA.** This is an "aneurysm of latency." In spite of the many possibilities for the production of respiratory, esophageal, or vertebral symptoms, this type is especially liable to be overlooked. The frequency of failure to discover aneurysm of this nature is due to the fact that the findings are frequently to be discovered upon the back, the examination of which is usually minimized. Anterior growth in the left sub-clavicular space is known. It should be emphasized that the location of the sac in the various forms is not pathognomic but only suggestive.

4. **ANEURYSM OF THE LOWER DESCENDING AORTA (THORACIC).** This is another aneurysm of latency differing from the above in merely the greater liability to pleural or lung rupture and a rarity to esophageal rupture. The fourth class does not merit distinction from the aneurysm of the upper descending aorta but it was thought advisable to retain the conventional terminology.

Symptomatology of Aneurysm of the Aorta. PAIN. In 1011 cases the symptomatology was noted. Pain was the first and chief complaint in 29 per cent. It was regarded as located in the chest in 18 per cent, left shoulder 4 per cent, right shoulder 3 per cent and in the back 4 per cent. For these reasons, the location of the pain should not be considered diagnostic. Since the pain may be felt in a variety of locations, any obscure pain in this region should excite a suspicion of aneurysm. In the absence of pulsation or swelling, pain in the precordia is often diagnosed as angina pectoris. Pain in either shoulder or back is often designated by the confusing and meaningless term "rheumatism." The importance of this is realized at once when we see rheumatism heading the list of wrong diagnoses. Pain in the intercostal spaces is often labeled neuralgia whereby a symptom is confused with a disease.

TYPES OF PAIN. For the purpose of clarity, the pain will be described as manifesting itself in one of three forms.

(a) *Anginoid.* This is apt to occur early in the disease. In the majority of cases, the anginoid pain is associated with aneurysm of the sinuses of Valsalva or the ascending aorta. Opinions as to the cause of the pain vary. From the different schools may be cited the following: (1) Involvement of the nerve plexus in the wall of the aorta; (2) stretching of the aorta; (3) pressure upon the coronary arteries. Like angina pectoris, it is often radiated down the arm and associated with numbness or tingling in the fingers. Exertion is especially apt to provoke an attack. The great importance of remembering this expression of aneurysm is seen when we recall that it is practically indistinguishable from pain of simple syphilitic aortitis or non-syphilitic angina pectoris. By this last phrase, the writer endeavors to include all of the diverse forms of disease which may present pain in the region of the heart. It makes an appearance at a time when other symptoms are apt to be absent and if disregarded and misinterpreted spells consternation for the unwary physician. Aneurysms associated with pain of this nature are prone to rupture by sudden physical exertion without further warning so that muscular effort must be curtailed.

(b) *Pressure Pain.* The typical pain of aneurysm is not present until the growth reaches the chest wall. It therefore comes late in the life history of aneurysm. Eroding pain is best seen in the descending and thoracic types which are often latent until late in the course. Many writers have noted that pain due to erosion of the ribs and sternum is much less marked than erosion of the vertebra. It is still more remarkable and not rare to see very decided erosion occurring without any pain at all. In addition to erosion, "pressure pain" may be seen when there is involvement of nerve trunks. This is particularly liable to be "neuralgiac" in character and often aneurysms of the descending aorta may present themselves under disguise of an intractable neuralgia. Finally, there may be pressure

pain when there is pressure upon any structure in the thorax so the old axiom that any pain not corresponding to definite disease of the thorax should excite a suspicion of aneurysm, has much truth in it.

(c) The third type of pain is difficult to name and occurs in dissecting aneurysms. It is a sudden terrific pain in the chest, usually associated "with collapse from which the patient may or may not rally." Radiation into the chest, abdomen, back, or shoulders is common while no report of an instance in which the pain passed into the arms can be found. When cases live for more than a few minutes, they present usually the clinical picture of a severe angina pectoris and in a short time (hours or days), they have a second attack and death. In exceptional instances, death has been delayed and case reports are not unknown which describe an attempt at an endothelial lining of the dissected channel. Many cases of double aorta are in reality this type of aneurysm.

DYSPNEA. This symptom is seen in a variety of degrees and types. It is the most common symptom of aneurysm, being the first or chief complaint in 31 per cent of the cases. It is placed second here because in its milder forms it is apt to be disregarded by the patient and elicited only upon inquiry. In its mildest and most common form, it consists of a mere substernal oppression, is increased upon exertion and indistinguishable from syphilitic aortitis. More severe is the form due to pressure upon the trachea and large bronchi expressed as dyspnea steadily increasing in severity. Either of the above are exceedingly liable to be diagnosed "failing heart" (in fact, part of the symptoms are due to circulatory disturbances in the lungs, either from the impaired valves or from passive congestion due to pressure upon the bloodvessels). There is a paroxysmal type of dyspnea which is very important. These attacks may be occasioned by changes in posture and the patient often assumes unusual positions in order to avoid their production (pain may also be relieved by posture). The cause is not known, some attributing the symptom to pressure upon the vagus, others the recurrent laryngeal, but whatever its ultimate etiology it is rarely seen unless there is actual pressure upon the trachea or large bronchi. The fact that asthma is third in the list of wrong diagnoses emphasizes the great importance of this symptom.

COUGH. This is the third great symptom of aneurysm, being the first symptom or chief complaint in 19 per cent of the cases. Like other symptoms it varies in degree and type. The commonest form is seen in association with "attacks of colds." A very frequent history is that the patient has in the last few years been having attacks of colds, the last one of which has persisted or is becoming worse. This is found as the first symptom in 10 per cent of the cases. These are frequently diagnosed as chronic bronchitis or winter cough (?). Brassy, gander cough is present and quite characteristic in only a minority of the cases. As a rule, it is present when there

is involvement of the recurrent laryngeal nerve which practically restricts it to arch aneurysms. Since the symptom occurs in only a minority of instances while its presence is suggestive, its absence means but little.

SPUTUM. This can be considered along with cough. Usually when gander cough is present, there is little or no sputum. When arch or descending aneurysms press upon the left bronchus, an exceedingly common occurrence, a large amount of sputum may be noted. The resultant bronchorrhea is in most instances associated with some bronchiectasis or low-grade infection in the area beyond the obstruction. When sputum is present, it is modified in about one-fourth of the cases by the addition of blood (chief complaint in 2.9 per cent). This bleeding may be of three types: (1) A large hemorrhage due to ulceration through the left bronchus or less commonly the trachea which is fatal in a few minutes; (2) a group in which profuse hemorrhages are seen over a period of months due to leaking of the aneurysm and subsequent blocking of the rent by means of a clot; (3) those cases which have a low-grade tracheobronchitis, a passive congestion from a failing myocardium, pressure, pulmonary infraction, or actual rupture into the lung substance. The last two are relatively unimportant since they occur just before death. The association of cough with loss of weight, hemoptysis, and fever makes tuberculosis second in the list of wrong diagnoses.

TUMOR. This is at times the chief complaint and may be one of the early symptoms, especially in arch tumors growing forward. As a rule, it is overemphasized as a symptom since at the time it appears diagnosis can be made by a tyro. The process may be painless but unfortunately for the sufferer this is quite unusual. As a rule, tumor is not an early symptom and in many cases may be absent throughout the entire course of the disease. When the pulsating tumor has appeared, a diagnosis is rarely in doubt because at this late stage most of the other symptoms or signs will be well marked. Pulsating empyema has caused confusion in a few instances.

DYSPHONIA. A common symptom in arch aneurysm is dysphonia, but is a chief complaint only one-sixth as frequently as pain. The voice may assume any character, usually husky or hoarse although it may be "cracked, tremulous, or even aphonia" may be present. Dysphonia is important as a symptom because it is indicative of the location of the lesion and not because of its extreme frequency. It rarely causes diagnostic difficulty because this symptom is rather well understood. In a few cases the diagnosis was tuberculous laryngitis or chronic laryngitis. The symptom was absent in one-fourth the cases in which it was mentioned. Cord changes antedate voice abnormalities.

DYSPHAGIA. This symptom is closely allied to dysphonia. In arch aneurysms it is produced by pressure through the bifurcation of the trachea. The lower the aneurysm is upon the descending

aorta, the less frequent is dysphagia. As a chief complaint it is not common, being found in only one-half as many cases as dysphonia. Dysphagia was absent in 46 per cent of the cases in which it was mentioned which is somewhat surprising since rupture into this structure is third in frequency.

LOSS OF WEIGHT AND APPETITE. The first is much more common than the second. Loss of weight is the chief complaint in 1.9 per cent while loss of appetite is the chief complaint in 0.5 per cent. As would be expected, these symptoms are present only in those cases which have lasted over a period of time. Loss of weight may be due to a number of causes. Among them are: (1) Pain anywhere in the thorax; (2) pain on swallowing, and more rarely (3) pressure upon the thoracic duct. Loss of appetite while uncommon may be a prominent feature in some cases.

PALPITATION. Among the common symptoms will be found palpitation, ranking at about the same level as dysphonia as a chief complaint. Unfortunately it has no peculiar feature which seems to differentiate it from other types of palpitation.

FEVER. This is not really a symptom but a complication. It must be emphasized as important since with bronchostenosis and subsequent bronchiectasis, low-grade infection is not at all rare. "Chronic pneumonias" are a frequent cause of death. Other symptoms of less importance are, disturbances of sweating, herpes, hiccough.

PULSATION. Among the most important objective phenomena is found pulsation. Although rarely a chief complaint, it is more common than tumor as a finding. The first type of pulsation is the diffuse general shock that may be seen anywhere in the chest. It is particularly frequent in ascending aneurysms complicated by cardiac hypertrophy due to a concomitant aortic regurgitation. Cases having a large mouth to the aneurysm may have pulsation over the sac. The second type of aneurysmal pulsation is diffuse. It differs from the preceding in that no distinct shock is noted. Pulsations are most frequently noted in the second right or left intercostal spaces or in the back. With the exception of the last, pulsation is not in any way characteristic of aneurysm. Broadbent's sign may give rise to confusion but is not a pulsation but a tug. Pulsation in the back should be emphasized since this group of cases often have but a few other symptoms. Expansile pulsation is often noted late in the development of the aneurysm, but is a tactile rather than visual impression.

CYANOSIS. In ascending aneurysms there is great opportunity for pressure upon the superior vena cava, the pulmonary artery or the right auricle, while in arch tumors, there is the same liability to pressure upon the innominate vein, the subclavians or the jugulars. In the descending form, the azygos system may be involved. In reference to the superior vena cava, it is surprising how nearly

complete obliteration may be found without marked symptoms. Should rupture occur into either vena cava, the pulmonary area or right heart, cyanosis may be a marked finding. Pressure upon the other vessels mentioned causes cyanosis in the areas which they drain. Closely allied to cyanosis is visible enlargement of the veins. Peculiar pictures may present themselves; as unilateral cyanosis of the head and neck (jugular compression) involving one arm (subclavian compression) or the head, neck, and arms (innominate or superior vena cava compression). In some cases we find the intercostal mammary group of veins enlarged (compression above the azygos major) or again the anterior chest wall may show a dilated plexus of veins and edema of even the posterior thoracic wall (deep cervical intercostal communication). Compression of the azygos major is not rarely a cause of right sided pleural effusion which not only adds to the patients' discomfort but helps to obscure the diagnosis. Inferior vena cava compression is not common.

OCULAR PHENOMENA. Ocular symptoms although well known should be mentioned because of their frequent absence. They are absent in over one-half of the cases in which they are mentioned as a symptom. Aneurysms irritating the superior cervical sympathetic may show dilated pupils, widened slit, protrusion of the bulb, or in the stage of paralysis may be seen miosis, exophthalmos and sympathetic ptosis. Changes in the size of the pupils may be caused by vascular conditions. More important than dilatation or contraction is a variance in size in the two. Separate and distinct from the vascular disease, pupillary findings due to the concomitant luetic involvement of the central nervous system may be present. As in the case of other symptoms, positive findings are suggestive while negative findings should occasion no wonder.

INVOLVEMENT OF THE RECURRENT LARYNGEAL. This sign is frequently overlooked because of, either the inability to make the examination or, more commonly, neglect. It might be expected from the location of the laryngeal nerves that arch aneurysms might produce changes in their function. When involved, it is usually the left that is disturbed, more rarely the right and still more unusual is involvement of both. As a rule the cord may be paralyzed a considerable length of time before there is any voice change. Later when the cord passes back into the "cadaveric" position the various types of dysphonia appear. It is therefore important to examine all the vocal cords of aneurysm without waiting for voice changes since cord changes as a rule precede and outnumber in frequency voice changes.

Physical Signs. PALPATION. All the above symptoms and signs belong properly under inspection with the exception of expansile pulsation. Among the other very important findings of palpation are those variations found in the pulse. From a theoretical standpoint the pulse in the aneurysmal sac should be later than the apex

impulse but since the time interval is so short this sign gives practically little information. Palpation of the various arteries may give some information but since palpation is usually confined to the radial artery, aid from this method is unusual. In case reports, observation of the pulse is mentioned about as often as the pupils but the first more frequently shows abnormality. Inequality of the radial pulses in aneurysm has long been known but as a matter of fact this examination is rarely done unless other signs of aneurysm are manifest. As a rule the pulse is smaller upon the side of the aneurysm. While testing for inequality of the two pulses not rarely will be noticed what appears to be a delay of one of them. The delay is usually found in the smaller pulse. Many types of tracings have been devised for the radial pulse but since a tracing of a single pulse gives nothing more than simple palpation this mode of examination might easily be omitted. Simultaneous tracings of the two radials is desirable when the exact location of the aneurysm is necessary, as for operative purposes. As might be expected from the above description of the pulse, variation is dependent partly upon the size of the sac and even more upon the character of its contents. A sac even though large, filled with a laminated clot, dampens the pulse but little.

TRACHEAL TUG. Ever since Oliver noted this phenomena the literature has had many reports upon this sign. The directions for eliciting it are too well known to need repeating. It is positive when the aneurysm presses upon the left bronchus or the trachea near the left bronchus and is most marked during inspiration. It is positive in much less than one-half the cases because of the anatomical requirements for its production. A few authors, especially Sewall, have pointed out that slight degrees of this phenomenon may occur in other conditions. For example in solid mediastinal neoplasms, in cases of tracheobronchial lymphadenopathy and it is not at all rare in pulmonary tuberculosis or left pleural involvement. Any condition anchoring the left bronchus to the aorta may produce this sign. Attention has been directed to the presence of this sign even in enteroptosis (Wenckebach). Briefly, it should be remembered that this symptom is absent in over one-half the cases and may be present in slight degree in other conditions.

PERCUSSION. In percussion we have a most important finding, namely, dulness. In a majority of instances it is sub- or parasternal. As mentioned in the beginning of the review, aneurysms of the sinuses of Valsalva may never reach sufficient size to give rise to changes in dulness. However, ascending aneurysms with their large sacs will usually give rise to dulness to the right of the sternum. Arch aneurysms when not too deep will give rise to substernal or left parasternal dulness. However, mere dilatation of the aorta may give rise to this phenomena. In descending aneurysms the dulness may be found in the subclavian space, the axillary space or,

more commonly, in the left interscapular and left subscapular space. It is amazing how rarely posterior dulness is mentioned in case reports although nearly every text-book has emphasized it. Smith's tracheal percussion has never come into general use.

AUSCULTATION. The findings derived from auscultation are of two varieties: (1) The heart and aorta and (2) the lung. Examination of the heart may show the signs of aortic regurgitation, which often accompanies sinus aneurysms. As to the aneurysm proper there are several factors which make for variation in auscultatory findings. Adventitious sounds depend upon the contents of the sac and the conditions at the orifice. Among the positive findings one notes a dull first sound followed by a ringing accentuated second sound. Occasionally one hears a systolic "humming-top" murmur which is found in cases having a communication between the aneurysm and the superior vena cava, the pulmonary artery, or the various heart chambers. A bruit over an aneurysmal sac is not an important finding since it is absent in a great number of cases. Like many other findings its presence is additional evidence while its absence in no way influences the diagnosis.

In reference to the lungs are those findings associated with bronchiostenosis such as lagging respiration, diminished expansion, later, the findings of bronchiectasis, although as a rule these are not decided. Finally the signs of low-grade infection manifest themselves. There may be merely a diminished respiratory murmur or in other instances the sound may be entirely absent. Findings of a pleural effusion or the pneumothorax may be superimposed upon the other lung signs.

Incorrect Diagnosis. Some of the reasons for making wrong diagnoses have been suggested. The incorrect diagnosis was noted in 130 cases.

Rheumatism	32	Failing heart	10
Tuberculosis	22	Mediastinal neoplasm	10
Asthma	18	Endocarditis	4
Chronic bronchitis	14	Angina pectoris	4

Pericarditis, pleurisy, carcinoma of stomach and esophagus, chronic laryngitis, tuberculous laryngitis, abscess of the lung, pleural effusion, and empyema each 2.

Duration of the Symptoms. In reference to this point, 830 cases were studied. These were not selected. The first large group consists of 312 cases, in which the duration was under three months. This figure is undoubtedly high since those cases in which death was the first symptom are much more apt to be reported than those which run a prolonged course. Of the aneurysms which run so short a course, there are two main types. The first are the aneurysms of the sinuses of Valsalva which are prone to early pericardial rupture. The second are the "early" deaths due to undetected descend-

ing aneurysms. It does not seem probable that the course of aneurysm is so dismal that one-third of the cases die in three months but more reasonable to suppose that statistics like those of Lemann, where death was not the first symptom and where more careful observation than the average reported case received, are more nearly correct for this first group.

0 to 3 months	312	5 to 6 years	14
4 to 12 "	234	6 to 7 "	6
1 to 2 years	128	7 to 8 "	6
3 to 3 "	70	8 to 9 "	6
3 to 4 "	22	9 to 10 "	4
4 to 5 "	8	10 to 20 "	18
		10 to 30 "	2

The roentgen-ray is diminishing the number of cases which are discovered for the first time in the postmortem room. In spite of the fact that a great majority of the cases die within a two-year period, it is better to look at the table from another angle. Just as we may expect to see aneurysm at any age, so must we expect it to last a variable time.

Death in Aneurysm. Death in cases of aneurysm may be due to one of three causes. The first consists of those cases which die of some disease separate and distinct from the aneurysm. This group needs no discussion. For convenience the remaining two causes may be described as those which die from rupture and those from the mechanical effects of the sac. About 52 per cent of the cases die from rupture.

TABLE I.—TABLE OF RUPTURES INTO THE VARIOUS ORGANS.

	No.	Per cent.		No.	Per cent.
Pericardium	369	31.0	Right lung	12	1.0
Left pleura	174	14.6	Right bronchus	12	1.0
Esophagus	112	9.4	Right ventricle	12	1.0
Right pleura	88	7.4	Left auricle	9	0.7
Left bronchus	85	7.1	Descending vena	8	0.6
Trachea	74	6.2	Left ventricle	5	0.4
Externally	61	5.1	Spinal column	4	0.3
Pulmonary artery	45	3.7	Hematoma thorax	4	0.3
Sup. vena cava	44	3.7	Stomach	3	0.2
Left lung	40	3.3	Both pleura	2	0.1
Mediastinum	20	1.6	Hematoma neck	1	0.8
Right auricle	13	1.0			
Total				1197 ruptures	

Ruptures have certain interesting features. In the first place there is a high percentage of pericardial ruptures. These outnumber the instances of either left or right pleural rupture, but since they contain features in common, they may be discussed together. Ruptures into serous surfaces are extremely apt to occur without warning, and usually the tear is sufficiently large so that death occurs in a very short time (minutes or hours). As stated above the

rupture of this nature is extremely apt to occur at the time of sudden violent muscular effort, although reports were noted in which the case was found dead in bed or in a chair. Esophageal ruptures, like ruptures through other mucous membranes, are apt to be a slower process and frequently give repeated warning. Oozing over a considerable period of time is not uncommon and the diagnosis of carcinoma of the stomach or esophagus has been made in some cases. At the time of the hemorrhage or a profuse hemorrhage followed by a second after an interval of ten to twelve hours. Ruptures into the bronchi or the trachea are apt to be quite similar to esophageal. Occasionally there may be an immediately fatal hemorrhage but more commonly repeated slight hemorrhages or oozing

TABLE II.—TABLE OF RUPTURES INTO VARIOUS ORGANS.

	Asc. (365) per cent.	Arch. (226) per cent.	Desc. (125) per cent.	Thor. (50) per cent.
Pericardium	57.5	12.8	..	2
Left pleura	2.1	12.8	30.4	46
Esophagus	1.6	12.8	19.2	14
Right pleura	3.0	10.1	9.6	12
Left bronchus	0.2	13.7	23.0	4
Trachea	0.8	16.3	4.8	
Externally	4.9	3.8		
Pulmonary artery	10.1	1.3		
Sup. vena cava	8.4	1.7		
Left lung	0.5	3.5	4.8	10
Mediastinum	1.5	3.5	2.4	2
Right auricle	3.0			
Right lung	0.8	1.7	0.8	
Right bronchus	0.5			
Right ventricle	2.4			
Left auricle	0.2	0.8		
Left ventricle	0.8			
Spinal canal	1.6	4
Hematoma	0.4	0.8	
Stomach	0.4	..	4
Both pleura	0.2	0.4	0.8	2
Hematoma of neck	0.2			

over a period of time. Profuse bleedings with a long period of comparative freedom from hemorrhage is not rare. External rupture is probably more dramatic than those which have been described above. It must be emphasized that this is not a common termination of aneurysm. Usually the aneurysm points, not unlike an abscess (for which they have been lanced). Even when definite pointing has occurred, it is by no means assured that external rupture will occur. At times the aneurysm will "weep" externally for weeks and then end in rupture into some other structure. In rare instances the aneurysm ruptures into the subcutaneous tissues and subsequent gangrene occurs. Rupture into the pulmonary artery is one of the types in which a fatal issue may be delayed. When this occurs in addition to the signs of aneurysm, there is

sudden onset of cyanosis, orthopnea, the systolic "humming-top" murmur, or thrill. Edema of the upper extremities and head is by no means constant. Rupture into the superior vena cava has been well described by several authors and shows: Sudden onset with pain, dyspnea, some shock, feeble pulse with sweating, then cyanosis and swelling of the upper extremities, and a similar murmur and thrill as was mentioned under rupture into the pulmonary artery. When rupture occurs into the lung there may be either a rapid death from hemorrhage or a slower death from a "chronic pneumonia." Mediastinal ruptures offer no peculiar features, while those into the chambers of the heart resemble quite closely congenital heart disease. Spinal cord involvement by rupture is rare and unusually shows a rapidly advancing paraplegia. In rare instances rupture may take place into the stomach by dissection of the coats of the esophagus.

Conclusion. A study of 4000 aneurysms of the thoracic aorta has been made. The relationship to sex, age, age incidence in males and females was noted. The location of the lesion, the symptomatology, the physical signs, duration of symptoms, types of wrong diagnosis, location of ruptures and causes of death were studied.¹

PROBLEMS IN HYPERTENSION—AN ATTEMPT TO CORRELATE HYPOTHETICAL AND PRACTICAL CONSIDERATIONS.*

BY SELIAN NEUHOF, M.D.,

NEW YORK.

STARTING from the fundamental observations of Bright down to modern studies in blood-pressure, blood chemistry, functional renal tests, renal pathology and physiology, there is perhaps no domain of internal medicine upon which more intensive work has been done, than upon the kidneys. Clinical hypertension in terms of renal pathology is one of the comparatively modern phases that is at present being constantly attacked and studied. Yet with all the amassed and voluminous literature and data on just this one phase of the problem—chemical blood investigations, experimental production of nephritis by injection of specific kidney poisons, and more recently by protein overfeeding; clinical studies of functional renal disease; finer studies of kidney pathology, there are but very

¹ The writer wishes to express his indebtedness to Dr. Aldred Scott Warthin, Director of the Pathological Laboratory, University of Michigan, for permission to examine the records of cases occurring in his service, and to Carl Vernon Weller, Professor of Pathology, University of Michigan, for reading the manuscript and many suggestions.

* Read before the Eastern Medical Society, New York City, December 14, 1923.

few definite, indisputable, fundamental facts and concepts that have withstood assault. At least one positive statement may be made, namely that pathological hypertension in its final analysis is due to contraction of the systemic arterioles and capillaries, for as recently demonstrated (especially by Krogh), the immense capillary bed is also under the influence of nerves which can and indeed do profoundly influence the blood-volume in various areas of the body. Of immense importance is also the fact that capillary constriction does not necessarily go hand in hand with arteriolar constriction or with the independent contractility of capillary areas. For example, the arterioles of an area may show constriction, and the corresponding capillary bed may show dilatation. It seems to be the prime function of the capillary motor mechanism so to shift the intimate blood supply of tissues that up to a certain pathophysiological limit, the capillary blood supply, and therefore nutrition, is shifted where tissue economy needs it, be it in contracting muscles during work, in the gastrointestinal canal during digestion, and the kidneys at the height of their function. The interrelated nerve paths of these capillary motor nerves are at present entirely unknown.

It is fairly well recognized that arterial and arteriolar disease may be general and widespread, attacking the retinal and cerebral arteries, the aorta, kidneys, and pancreas and abdominal vessels; (general arteriosclerosis, atherosclerosis and arteriocapillary fibrosis) or the disease may attack and limit itself to the arteries of one organ predominantly and exclusively (usually in such instances the heart or the kidneys); or finally the disease may pick out and select just one or more of the principal arteries of an organ, for example, the aorta and coronaries, almost to the entire exclusion of the remainder of the cardiorenal vascular system.

In order to correlate certain clinical observations, I have divided hypertension as found clinically into certain groups; these cover the majority but by no means all hypertensive conditions. And it shall be my problem, in the light of physiological, pathological, experimental and clinical data, to try to discover, and, where necessary, to theorize frankly as to the possible basic, etiological "insult" for the hypertension.

I may interpolate here that instead of the term, essential hypertension, I prefer the terms hyperpiesis or functional hypertension, because if they have any precise significance at all, they refer to high blood-pressure without any known or discoverable pathological organic basis, and they are advisedly non-committal on the question of benignity or severity. I believe furthermore that essential hypertension is an especially inapt term because it has already been given so many meanings, hence it must be or should be exactly defined each time it is used. And when used in the sense of high blood-pressure without organic basis, functional hypertension conveys the idea more definitely.

In this paper hypertension will be regarded as consisting of a systolic blood-pressure of 150 or over.

Returning now to the groups we have:

1. *Abnormal Vaso-constrictor Influences Originating from the Higher Cerebral Centers.*

As is well known there are many pressor and depressor fibers in the nerves that reach the vasoconstrictor center in the medulla. Stimulation of the pressor fibers produces contraction of the peripheral vessels with increased blood-pressure, while stimulation of the depressor fibers produces a reverse influence, that is, peripheral dilatation with decreased blood-pressure. Furthermore mental work produces constriction of the skin arterioles, a depressor influence. "In both instances we must assume intracentral paths between the cortex and the center in the medulla."² As further bearing upon psychic vascular reactions, Krogh¹ has shown that an unnarcotized rabbit's ear properly prepared for microscopic study will not redden or blanch if the animal remains quiet. If, however, the animal be suddenly frightened or disturbed, often the ear first blanches and then reddens, palpable examples of arteriolar and capillary constriction and dilatation, respectively. Section of the dorsal sympathetic abolishes this reaction, hence the efferent paths probably follow these nerves. By analogy, it seems probable that pallor accompanying human emotions "is produced in the sympathetic tone of the small skin vessels, while blushing is due to a reflex relaxation of this tone."¹ Bearing these physiological and experimental facts in mind, it comes within the realm of clinical probability that an excitable, volatile individual, one who is constantly harried and worried and hurried in his daily routine may send abnormal excitatory influences from the brain through various efferent paths, thus inducing vasoconstriction, if only momentary, of the arteriolar and capillary beds, in other words, causing what we clinically measure as hypertension. On the other hand there are individuals who do not betray their excitement by external manifestations, but who make abnormal conscious attempts to hold themselves in check. Both are instances of what may be called potential vasomotor instability. I have not found them to be of an especial type of physique or habitus; they are neither predominantly stout, lean, obese, tall, or squatty. I conceive that such individuals may have hypertension, at least temporarily, even without the organic background of actual pathological cardiovascular renal disease; or if the latter already be present, such abnormal excitation may continue hypertension in such patients, indeed they may react more readily and consistently to any hypertensive influence. Thus the psyche of an individual is to be seriously reckoned with and weighed in its clinical application, in order to assess what may be termed the psychic component of such hypertensive cases. This viewpoint also serves to explain how patients of volatile or with

wilfully suppressed emotions—the typical rushing American business man, as an example of the former; the moody anxious individual of the latter—are so much benefited when they are ordered away from town and from business for a few weeks. Given a happy prognostic outlook, and provided there is no inordinately severe organic cardiorenal basis for the hypertension, they often feel very well and are capable of much physical exertion as in golfing, rowing and walking. This symptomatic improvement, especially in reference to dyspnea, dizziness and precordial uneasiness does not necessarily imply that there is always a corresponding decrease of blood-pressure but a degree of physical comfort, a happier outlook is given these patients which they retain when they are again enabled to take up their work in whole or in part.

2. *Reflex Influences Emanating from Aortic Disease.*

The aorta, as is known, is surrounded by many plexuses and nerve filaments, important branches of the vagus and sympathetic. I believe that the important significance of this rich net-work of nerves as originators and carriers of abnormal excitation to the vasomotor center has been almost entirely overlooked.

That hypertension can exist with cardiosclerosis, but without sufficient coincident renal disease to account for increased blood-pressure has again been recently emphasized by Moschkowitz.³ In the 5 cases that he studied postmortem, the renal lesion was not of sufficient moment to be a factor in the hypertension; but widespread disease of the heart and its bloodvessels—aortitis, ventricular hypertrophy, scar tissue, coronary disease—was a feature in various amounts and degrees. Some clinical corroboration that isolated aortitis can cause hypertension is found in instances of luetic aortitis in which during the inflammatory recrudescence of the disease (a recrudescence aortitis), precordial pains, hypertension and bronchospasm occur, to again recede with recession of the inflammation. As Longcope states,⁴ hypertension in such instances can scarcely be explained by pains or cyanosis “for pain is frequently absent, and dyspnea may continue for some time (fifteen to thirty minutes) after the sudden drop in blood-pressure which comes with the relief of acute symptoms.” He speaks, however, of a paroxysmal type of dyspnea found in luetic aortitis, and compares this to what occurs in the experimental animal. I conceive that a lesser degree of bronchospasm and hypertension may occur in less acute cases. Thus in a patient of mine with typical well-compensated luetic aortitis, the usual blood-pressure was 170 systolic. Following a coryza, the patient developed asthmatic breathing, although not severe enough to be characterized as paroxysmal. During this time and until the symptoms came under control with less wheezing and coughing, the blood-pressure was from 150 to 160 systolic. Later, when the bronchial spasm and pain had practically disappeared, the systolic pressure was around 112. There was no

decompensation. This, then, is an instance of moderate hypertension in a patient with luetic aortitis and severe bronchial spasm, apparently induced by abnormal reflexes arising from a diseased aorta.

Instances of pure aortic disease with hypertension are typified in those cases of rheumatic aortic regurgitation in the young, with or without advanced ventricular hypertrophy. Here there is surely no evidence, clinical or pathological, of kidney involvement as a factor in the production of high blood-pressure, nor of course, does generalized arteriosclerosis play a role. The hypertension is not extreme, usually between 170 and 190; the diastolic pressure is very low or zero. Perhaps one in 3 or 4 cases of typical rheumatic aortic regurgitation, well compensated, with throbbing carotids and a Corrigan pulse presents this picture of hypertension. The vasomotors are labile. The blood-pressure may be 150 one day or at one time, and at the next examination, perhaps a few hours later, the pressure may be 180 or 190 with no difference in the physical or symptomatic status of the individual. What influences ventricular hypertrophy with its attendant cardiac hyperactivity may play in the production of this type of hypertension one cannot state dogmatically. At any rate, it seems probable that the prominent factor lies in the continuous "insults" produced by the continued tremendous aortic fling that hyperexcites the nerve mesh encircling the aorta. Perhaps ventricular hyperactivity with its blood fling is an added factor. The physical evidence of this aortic fling is readily derived by fluoroscoping a typical case of rheumatic aortic regurgitation.

The physiological principle that nerve impulses transmitted to the medulla act in maintaining the nerve tone of the vasoconstrictor center is now generally recognized,¹ yet that would scarcely explain how hyperexcitation of the nerve mesh surrounding the aorta in cases of rheumatic regurgitation and of syphilitic aortitis produces hypertension, for it is well known that undue stretching of the aorta excites the depressor, not the constrictor mechanism to action. On the whole, it seems probable that general tissue anemia from improper vascularization resulting from aortic disease, with its concomitant myocardial disturbance, may cause a pathophysiological response in the manner already pointed out, namely, sufficient vasoconstriction in some arteriocardillary areas to bring about clinical hypertension. In other words, although the nerve paths are unknown, vasoconstriction seems one of nature's peripheral provisions for deflecting more blood into an improperly nourished area by sufficiently constricting other arteriocardillary beds or bed, thus raising the blood-pressure.

3. *Reflex Influences Emanating from Coronary Disease.*

I refer here to individuals who present no general symptoms of advanced cardiorenal mischief, no abnormal signs, no dyspnea, no

cardiac enlargement, no decompensation, no urinary changes, no marked decrease, if any, of phthalein output, and who, on the whole, look robust and well preserved. They do present, however, two cardinal signs, hypertension (usually moderate) and precordial pains. The hypertension is not always constant, as is shown in the following case. Hypertension was present for a while some years ago and then disappeared. Indeed, although coronary disease was suspected from the beginning, quiescence of symptoms for years, normal blood-pressure and normal physical signs at later examinations lessened the impression of severe disease until death suddenly occurred.

The precordial pains of individuals in this group are usually not constant; they are marked by remissions and by occasional severe exacerbations in one of which the patient may suddenly die. The usual localizations of the pain are near the cardiac apex or at the midsternum, sometimes radiating to the back. They are present especially when the patient walks after meals, or when walking or driving against cold winds. Often the pains are so correlated with gastric symptoms, especially belching and pyrosis, that it is difficult, indeed at times impossible to decide which is the primary offender, the stomach or the heart. Such patients will be discussed more in detail in the following group (Group 4). A typical instance of temporary hypertension with coronary disease is herewith epitomized.

Dr. S., dentist, aged fifty-four years, was seen by me for the first time seven years ago. At that time the chief symptoms were precordial pains and moderate hypertension. The patient was considerably worried, and he worked very hard. He was an excessive tobacco smoker. The roentgen-ray and the electrocardiogram revealed nothing abnormal. He was told to quit smoking and to work less intensively. As a result, the precordial pains disappeared, the blood-pressure became normal and the patient was much more comfortable. I did not see him again until shortly before his fatal illness. In the interim he had felt comfortable, had only occasional pains and was able to go ahead with his work in normal fashion. The recent history was that during the past few months he had more marked precordial pains, especially when walking in windy weather. He had a very severe attack of pain four months and again two weeks ago; the latter followed some aggravation. Since then he had frequently to stop walking because of pains in his chest. Examination at his home revealed no dyspnea, the patient was able to lie flat in bed; the entire cardiovascular and pulmonary examination, including blood-pressure revealed no abnormality. He was kept in bed and for a few days was quite comfortable. One night he was taken with very severe pains in the chest and died within two hours. This case is an example of entirely negative physical findings except moderate hypertension some years ago. More

attention to the symptoms rather than to the negative physical findings may have aided in making the proper diagnosis, namely, coronary disease.

What seems of especial importance in patients of this group is that as far as clinical findings are concerned, the coronaries bear the main brunt of the arteriosclerotic process. When there is no evidence of widespread cardiorenal mischief it will naturally require corroborative postmortem examinations in order to rule out other important contributive pathological factors, especially of aortic, myocardial and renal disease.

As one instance of disease confined chiefly to the coronary system, but especially to the small artery supplying the auriculoventricular node, I wish briefly to quote a case of a woman, aged eighty years, with heart-block. The main coronaries were somewhat thickened but patulous, the artery that supplied the node was entirely sclerosed and calcified and was surrounded by a zone of degenerated musculature. The remainder of the heart, the myocardium, valves and aorta, was particularly well preserved and free from sclerotic changes. This again demonstrates how arteriosclerosis may selectively attack special arteries, not necessarily an entire arteriolar system; and when such arteries are vital to an organ like the heart, such isolated disease may produce severe cardiac symptoms and finally death.

How shall we explain hypertension in cases of assumed isolated coronary disease? Illuminating experiments by Starling⁵ on the coronary bloodflow in the dog's heart show that if the coronary pressure be artificially raised, the heart, instead of becoming weaker, begins to revive, and the ventricular output increases, in spite of the necessarily increased work of the heart in overcoming the increased coronary blood-pressure. So also in another series of experiments, artificial increase of general blood-pressure increased the coronary output. Increased blood-pressure is apparently Nature's provision to increase the blood supply to the heart. Starling also states the vital necessity of proper coronary flow to insure proper oxygenation, proper tissue respiration and hence proper cardiac function.

What the actual mechanism is that increases blood-pressure in clinical instances of assumed isolated coronary disease it is impossible to state with exactitude. We know that the coronaries are richly surrounded and supplied with nerve plexuses and ganglia, and it seems highly probable that abnormal excitation originating from this rich nerve supply may reflexly excite and influence the vasoconstrictor center. On the other hand, coronary disease, when advanced, certainly decreases the blood supply to the peripheral tissues by depressing the pumping power of the heart. There is thus produced a struggle between different vascular fields. The sum total however must be a system with increased resistance;

thus a failing heart is countered in the peripheral vascular system by increased blood-pressure. This is again nature's provision for shifting blood-volume where needed for oxygenation purposes, always however with increased resistance, hence calling for more pumping power in order to force the proper amount through constricted arterioles, a true vicious cycle.

4. *Temporary Hypertension from Functional Cardiospasm.*

Patients of this group are usually stout individuals between thirty and fifty years of age who lead a busy active life, who continually rush about or are easily upset nervously, and who suffer from the clinical symptoms of mild cardiospasm: sensitiveness to pressure under the xiphoid, fulness and a tendency to belch. They usually bolt their food. There is sometimes a conscious feeling of food sticking for a moment at the cardia. Such cases of cardiospasm are mild and are not comparable to the occasional severe forms in which there is definite cardiospastic stricture of the cardia, with inability to pass normal sized bougies into the stomach. That mild cases exist, I demonstrated in at least one instance by roentgen-ray. The patient had epigastric tenderness, and distention and belching after meals. The barium mass after being swallowed was seen fluoroscopically to stick for several seconds at the cardia; there was reversed peristalsis for a few moments, the cardia then opened and the mass entered the stomach. While patients such as I have described have these outstanding gastric complaints, they also frequently complain of midsternal pains, which occasionally radiate to the left arm or to the back between the angle of the left scapula and the vertebral column. Another symptom which draws special attention to the heart is the fact that walking in the fresh air, especially after meals, is particularly apt to be followed by precordial and referred pains; added to this is moderate hypertension (usually from 150 to 180 systolic). Thus the clinical complex is one closely resembling coronary disease. But neither fluoroscopy, electrocardiography or phthalein output examinations, nor the ordinary methods of routine clinical examinations show any evidence of cardiac disease or decompensation.

A few examples will serve to illustrate this type: Mr. E. W. O., aged fifty years, has always been a quick and irregular eater, almost always bolting his food. For about two years, he has had mild dyspeptic symptoms; slight epigastric pain and belching after meals. His bowels are constipated. He has never vomited, his appetite has always been good. He is a moderate smoker. For about one year, he has had precordial pains, which of late radiate to the left arm and hand, and produce a sensation of tingling. Several times he has had to stop walking because of the precordial pains. He has also complained of headache and dizziness during the last six months; these symptoms are apparently not connected with his gastric complaints. Except for gonorrhea twenty-five

years ago, he has had no other infections. He passed a satisfactory life insurance examination one year ago. Of recent months he was told by his family physician that he has hypertension and true angina pectoris.

Examination reveals a stout individual. The pharynx is somewhat red, probably from smoking. He has some poor teeth. The systolic blood-pressure is 160, the diastolic 100. All the heart sounds are normal. There is no undue dyspnea or tachycardia after exertion. The lungs and reflexes are normal. There is no edema of the legs. Abdominal examination reveals slight but definite sensitiveness under the xiphoid. Orthodiascopic roentgen-ray examination reveals a normal sized aorta, with the heart lying flat upon the diaphragm. The electrocardiogram shows nothing of note. The urine is normal. The diagnosis of cardiospasm due to an irregular mode of eating was made. The precordial pains were regarded as caused by coronary spasm, not actual coronary disease. He was placed upon a bland, antacid diet and was admonished to eat his meals regularly and slowly. Atropin and an antacid powder were prescribed. He consulted me about once a week for several weeks. At the second visit, the systolic blood-pressure was 145; thereafter it came to normal (between 120 and 130 systolic) and remained so during the entire period of observation. The precordial and referred pains, and the dyspeptic symptoms quickly disappeared and when last examined, he felt perfectly well in every respect.

Mrs. H. S., aged forty years, has been suffering for years from gastric distention and belching, especially after improper diet. Several years ago and twice since, she had gastric attacks with temporary hypertension from 160 to 200; the blood-pressure became normal when indigestion ceased. Two days previously, the family physician found decided hypertension.

Examination: No cardiovascular symptoms; no previous infections; blood-pressure, 120 to 90; heart, very soft systolic at apex; somewhat accentuated second aortic at right base. Lungs, mouth, reflexes, urine, normal. Abdomen, slight epigastric sensitiveness. Orthodiascopic examination: First part of aorta slightly enlarged. Electrocardiogram: normal.

Diagnosis: No organic cardiovalvular disease, temporary hypertension, cardiospasm. Therapy: Patient may be active, avoid acids, bland diet, atropin sulphate, antacid powder. After a few days, the patient felt well and has continued so.

M. O., male, aged forty-three years, has always been very active, a quick eater, and never rests sufficiently. He is always thinking of business. He had been told he had hypertension, with pressure around 160. A trace of sugar was found once. He suffers from fulness and distention after meals and is much worried and does not know how to act about diet and general care. He has had no

previous infections, and no cardiac symptoms. He is walking most of the day and smokes three cigars daily.

Examination: Blood-pressure 160; very soft systolic murmur at apex; slight apical overaction. Abdominal examination, negative. Very lively reflexes. Urine normal. Orthodiascope, normal.

Diagnosis: No cardiovascular disease; hypertension from continual rushing and bolting food. Therapy: Atropin sulphate before meals, antacid powder after meals; take one hour for meals; go to country week-ends; rest in evening between six and seven. Prognosis: Very good.

January 20. Not improved because he did not follow directions.

April 29. Had been feeling well. Now again excitable and has headaches. Blood-pressure 140.

October 10. Slight recurrence of symptoms following nervousness about his father's health. Chief complaint, indefinite weakness in chest. Blood-pressure 150. Epigastric sensitiveness. Except for this spell, he had been well for months, with a normal blood-pressure.

It is difficult to correlate such abnormal excitation of the vagus branches supplying the lower esophagus and the cardiac end of the stomach, for cardiospasm is the outstanding clinical feature, as in itself a cause for hypertension, since physiologically vagus excitation results not in hypertension but in lowered blood-pressure. Perhaps both the cardiospasm and the hypertension are caused by abnormal cerebral impulses in these nervously excited individuals, and relief of the cardiospasm by atropin, and a quieter mode of living and of eating have the effect of calming these patients, thus relieving their hypertension. Therapeutic measures directed entirely to the gastric condition, proper food slowly eaten, rest for a while after meals, less rushing about, more mental quiet, not only relieves the gastric symptoms but also the hypertension. Atropin and an antacid powder are important therapeutic aids. The results of therapy are added proofs, I believe, that the source of trouble lies not in the cardiorenal system but in abnormal excitation of the vagus nerves that control the cardia.

5. *Hypertension with Auricular Fibrillation.*

This is well illustrated by the following case: Mrs. D., aged forty-seven years, does a great deal of physical labor in walking, carrying bundles and climbing stairs. She has had frequent attacks of bronchitis and of shortness of breath in recent years. Her climateric began two years ago. More recently she complained of severe dyspnea and had several fainting attacks. Examination shows auricular fibrillation, mild cyanosis, moderate hypertension and a heart slightly enlarged (roentgen-ray). The clinical diagnosis was moderate cardiosclerosis with superadded cardiac overstrain and climacteric hyperexcitability. She was given quinidin. The rhythm became normal after two days. The systolic blood-pressure

then was around 100 and remained at about that level during the time that she was under observation (several weeks). There was no decompensation with the lowered blood-pressure.

Hypertension in such instances of auricular fibrillation seems directly attributable to improper blood-mass distribution in the periphery, another instance of Nature's attempt to rectify circulatory instability by increasing pressure in some areas, thus shunting increased blood-volume in other more needed oxygen-poor areas, always, however, under the cardiac disadvantage of heightened blood-pressure. With normal rhythm and circulatory stability restored by quinidin, there is no longer need for Nature's safety provision and, where there is no advanced kidney disease, hypertension at once disappears.

6. *Hypertension with Endocrine Changes or with Exophthalmic Goiter:*

This refers especially to women at or near the menopause age and to cases of exophthalmic goiter. Regarding endocrine disbalance, hypertension here, at least in the beginning, must be regarded as of functional origin (so-called primary or essential hypertension), because nephritic or other pathological bases for the hypertension are almost always absent, and the hypertension is sometimes a temporary affair. Whether such hypertension can lead to actual nephritis is a very much debated question and will be discussed later. Theories regarding the cause of this type of hypertension are many; I need but mention the most popular, the hormones and adrenalemia, despite the fact that careful experimentation⁶ had not revealed any abnormal amounts of adrenalin in the blood. There is however, some experimental evidence that a pituitary hormone may be responsible for pressor influences in the blood.¹ In the search for physicochemical and hormone factors, however, attention has been detracted from perhaps the fundamental pathological conception, namely, abnormal excitability of the nervous system. Nervous hyperexcitability in these individuals is well characterized in the main by sweats, flushes and general irritability. And in cases of exophthalmic goiter—in addition to and more intense than these latter symptoms—is the added factor of overviolent and overforceful ventricular action and the flinging of blood into the aorta. This factor as influencing the aortic nerve mesh has always been described (Group 2). It is in brief, my assumption that hypertension at the menopause and in goiter can be more logically explained upon a basis of obvious vasomotor instability, for which, at least, there are a few indubitable clinical facts. How much this vasomotor instability may directly affect and cause the restiveness by vascular changes in the cerebrum, and indirectly by causing a vicious cycle, such as described in Group 1, are questions still *sub judice*.

7. Nephritic Hypertension.

This, the most important division I have left to the last. Reference is here to assumed or proven widespread pathological changes in the glomeruli, whether the predominant change be a chronic interstitial, the decrescent type of the arteriosclerosis of the old, or the large white kidney. It is becoming increasingly recognized that the kidney changes rarely run "true to type," and that transition forms are frequent. It is also a matter of common knowledge that hypertension does not proceed *pari passu* with the amount of kidney damage found at necropsy. Indeed, I have not infrequently found frank nephritics that feel better with for them, abnormal hypertension—200 or over—than when the blood-pressure is around 180. Nor can this be purely psychical, for there may be less dependent edema and less dyspnea at the higher than at the lower systolic pressures. This may depend upon the principles already referred to, namely that the physiological response has been more vasoconstriction in some areas and hence more blood-volume shunted in needed areas, despite the hyperincrease in blood-pressure. As a rule we find hypertension in those with advanced changes in the glomerular tufts (actual arteriocapillary fibrosis in the pathological sense); while with disease predominantly confined to the larger renal vessels (the renal arteries and their ramifications, the vasa recti)—a picture general in old arteriosclerotics with widespread degeneration of the larger systemic, superficial and deep vessels, hypertension is often absent.

In advanced nephritis with hypertension, blood chemistry often shows varying increases of the non-protein nitrogenous products; it is assumed that in these individuals the retained products act as poisons and produce hypertension, abnormal arteriolar and capillary spasm and constriction. Yet even this assumption does not aid in determining how these poisons so act. Perhaps an analogy from plant life, and some suggestive physiological and experimental data may throw some light on this vexed and vexatious question. Plants get their nourishment by osmosis from rootlets which ramify through the wet earth; this nourishment is brought to the stalk or trunk. In a human being the rootlets are the arterioles; the moist earth, the capillary bed and tissues. Cushny⁷ has estimated the number of glomeruli in the human kidneys as 2,000,000. If the twisted and bunched arterioles and capillaries so neatly packed by Nature into a small space of the kidneys were conceived as spread so as to resemble a capillary bed, one can only imagine the comparative immensity of such an arteriocapillary peripheral spread.

Arteriosclerosis has been variously described pathologically; the general pathological consensus of opinion is that it is not an inflammatory but a degeneration process. Disease of the glomeruli consists in thickening of the glomerular epithelium, and in fibrosis

and hyalinization and perhaps calcification of the glomerular tufts—"an arteriosclerosis in miniature."³

In an excellent experimental article, Richards⁸ has emphasized the importance of nervous stimuli in the experimental production of vasodilatation and constriction of the glomerular capillaries. Nerve filaments, presumably branches of the splanchnic ramify to the glomerular tufts. Nerve stimuli (and chemical substances) have been shown experimentally to exert influences upon glomerular afferent and efferent vascular tone. This much for the local glomerular reaction. Conceiving the glomeruli as a whole merely as a large arteriocapillary bed, there is, after all, no basic difference between abnormal excitation from partial or complete disease of such a renal peripheral bed with resultant (reciprocal) vasoconstriction in another capillary motor area than is found in Nature's numerous provisions for vasodilatation in some parts of the body, and vasoconstriction in others. Splanchnic vasodilatation after a meal, and peripheral vasoconstriction in other areas is a common example. That retained kidney poisons would or might be added factors is not only conceivable but is also probable; for once a break in physiological continuity occurs and actual pathology begins, there is freer play for the commencement—and once begun—for the continuance of a vicious cycle. Nature would seem to have started hypertension in order to force more blood in an organ beginning to be or already crippled by pathological changes. In addition the other component of the vicious cycle, retained renal poisons, plays a large role in these individuals, a fact reflected in the blood chemistry. In the decreascent type of the old, predominantly renal arterial tree changes (the vasorecti and their branches), since the peripheral renal arteriocapillary bed is not disturbed, there is no tendency to abnormal peripheral arteriolar excitation and its consequent vasoconstriction. Indeed these comparatively large arterioles although stiffened by disease, allow sufficient blood-volume to pass through, provided of course the pumping mechanism is still sufficiently powerful and efficient. Lack of resiliency of hardened arteries does not necessarily interfere with their caliber; the latter interference comes only with advanced thickening and calcification.

Another vexed question in hypertension is, which is to be regarded as the primary factor? Does, or can, functional hypertension cause nephritis, or *vice versa*? Klotz⁹ produced arteriosclerosis by suspending rabbits head down for prolonged periods. This experiment, though of course without comparable analogy in man, demonstrates perhaps that arteriosclerosis in the human being can be produced by too much pressure. An extremely suggestive point was made by MacCallum¹⁰ in a review on the subject of arteriosclerosis. Reviewing cauerimental and other factors, he states that the most important stial factors of arteriosclerosis are infections, intoxications

and unbalanced diets; that adrenalin injections produce arteriosclerosis (in rabbit's aorta) not merely as a hypertensive agent, but directly as a poison; that experimental methods of inducing hypertension may be divided into: (1) Mechanical means of raising blood-pressure; (2) chemical means of raising blood-pressure; (3) perverted diets. The first two he states, have failed to produce a type of arteriosclerosis comparable to that of the human being. Of the three groups, perverted diets have succeeded more regularly in producing arteriosclerosis experimentally, *especially when combined with mechanical disturbances*. Of these latter, increased blood-pressure (experimentally induced) is the only one of importance. In other words, increased blood-pressure produces arteriosclerosis experimentally only when combined with a factor (perverted diet) which causes actual kidney damage, *but alone it produces little or no change*. This statement is germane to our discussion, for it emphasizes well what I conceive happens clinically, that is, hypertension becomes a serious factor as a cause for nephritis only when there is with it some break, large or small, of physiological renal continuity. Therefore hypertension conceivably can cause nephritis, especially if one postulates the existence of an already pathologically damaged organ, whether such damage be microscopical or macroscopical. It is said that a 100 per cent normal kidney does not exist. This seems true in view of our knowledge that transient albuminuria is so common an accompaniment of febrile, tonsillar, exanthematous, toxic and other causes. Probably no one has escaped some such temporary kidney involvement who has lived to adult life. Who can say whether any permanent damage, no matter how minute, does not remain? In most cases the albuminuria clears up; in others, especially when tonsillar, febrile or other causes continue to recur, damage is added to damage until finally severe nephritic changes result.

And now, how shall we even theoretically explain permanent, continuing pathological damage in the vast majority of nephritic cases in which the toxic factor, whatever its nature, has ceased to act? The nephritis of scarlet is an excellent example; it undoubtedly is sometimes the beginning of a later severe nephritis, yet it usually takes years for severe damage to result. It seems to me that this is an important problem which we must attempt to elucidate. In this connection I wish to cite a suggestive article by Thalheimer¹¹ in which he attempts to prove that minute microscopical injuries to the cardiac valves, possibly the result of a mild toxemia, may finally eventuate, perhaps after years, in actual severe valvular damage, including verruci and even calcification. This he conceives results from slight, continuous mechanical insults—heart strain, improper minute aberrant currents, and so on, and not necessarily from superadded toxemias. The salient point is the assumption

of an original pathological nidus, the result of infection, protein poison, a toxic or dietetic factor, which causes loss of normal continuity, small or large, and which finally from *purely mechanical* reasons can eventuate into widespread pathological changes.

There are many theories regarding the fundamental cause of arteriosclerosis in the human being. Romberg¹² as well as Marchand¹³ regard the cause as fundamentally due to nutritional disturbances in the arterial wall, following disuse. Moschkowitz¹⁴ states that once hypertension is established many changes can be accounted for by "a mechanical stretching of the tissues with replacement fibrosis and eventually by hyalinization and calcification. The thickening of the intima, hypertrophy of the media and increase in the elastic fibers are probably in a great measure compensatory." This brings up the mechanical conception of the cause of arteriosclerosis, supported among older writers by Thoma, Traube, Rokitsansky and Marchand. Adami¹⁵ calls the process a "strain hypertrophy." Aschoff¹⁶ does not believe in the disuse theory as the cause of arteriosclerosis. Moschkowitz¹⁴ has suggested a mechanistic conception *without* however the important postulate of an *original pathological nidus*, however minute, as a starting point. With such a *locus minor resistentia*, given a tendency to hypertension, perhaps because of excitable temperament, or of abnormal renal products being retained, or indeed from any of the causes in the various groups already outlined, and in its trend, improper vascularization and improper nourishment to the kidney parenchyma, a vicious cycle may be started which in those disposed may conceivably produce far-reaching damage. And yet the beginning may have been as stated, a small microscopical change, the result of some temporary insult. Except as above mentioned, it is impossible to conceive how pathological mischief can continue after infections and toxemias have long ceased their acute damage, large or small. Replacement fibrosis, hyalinization, calcification, may after all be due to one fundamental cause, improper oxygenation with resultant improper tissue nutrition. Where there is already damage, even though microscopical, a *locus minor resistentia* is established. With this as a focus, all varieties of mechanical interference of the blood supply, contracted arteriocapillary areas, at the beginning not sufficient to cause clinical hypertension, can conceivably so further spread even microscopic glomerular damage that inevitably larger areas become affected. Finally there is that larger pathophysiological response of blood-volume shift so that ever larger arteriocapillary beds constrict to help shunt and supply the necessary blood-volume to the diseased glomeruli; at length the vasoconstriction is measured clinically as hypertension.

Why some individuals are "disposed" to kidney damage is again another moot question. Are some born with "weak kidneys" in a

morphological sense? Is it a fault in the germ cell? Is it a tendency to "bad vascular" tubing in the Osler sense, or is it after all poor terminal arteries, poor "rootlets," in the plant sense, rootlets that can no longer carry nourishment, and hence the organ slowly shrivels up and dries? These are queries which must for the present remain unanswered.

Summary. I have purposely been generic, hypothetical and sketchy, and have not entered into discussions of types of renal pathology. What I have attempted to do is to elucidate and correlate apparently contrary views, and have above all tried to find an underlying, fundamental cause which may perhaps tend to harmonize conflicting views; to show how functional changes may act and react upon an existent pathology, minute or gross; and how such morbid interactions, once established may eventuate into increasingly severe pathological destruction. Thus viewed, one may perhaps explain some common clinical facts such as the effect of toxins and infections in producing morbidity, and the effect of fundamental changes such as improper local vascularization in enhancing these morbid processes after the toxemia, using the term in its broadest sense, has long since run its course. Perhaps this problem can lend itself to experimental research; once establish that a pathological damage, already completed, can be made to spread by local or general vascular changes, changes which perhaps act fundamentally by undermining proper nutrition, and it will go far, I believe, in clearing up much that is misty and nebulous in the domain of cardiorenal-vascular pathology, and bring it in more direct line with actual clinical concepts and experience.*

REFERENCES.

1. Krogh: The Anatomy and Physiology of Capillaries.
2. Howell: Text-book of Physiology, 1924, p. 605.
3. Moschkowitz: Jour. Am. Med. Assn., 1921, **77**, 1075.
4. Longcope: Arch. Int. Med., 1913, **11**, 80.
5. Starling: Presse méd., 1922, **30**, 641.
6. Janeway and Park: Arch. Int. Med., 1910, **6**, 586.
7. Cushny: Excretion of Urine, 1917, p. 5.
8. Richards: AM. JOUR. MED. SCI., 1922, **163**, 1.
9. Klotz: Centralbl. f. allgem. Anat. u. Path., 1908, **19**, 535.
10. MacCollum: Physiol. Rev., 1922, **2**, 70.
11. Thalheimer: Arch. Int. Med., 1923, **30**, 321.
12. Romberg: Krankheiten des Herzens, 1909, p. 431.
13. Marchand: Verhandlungen d. Kong. f. innere Med., 1904, **21**, 23.
14. Moschkowitz: Jour. Am. Med. Assn., 1922, **79**, 1197.
15. Adami: AM. JOUR. MED. SCI., 1909, **138**, 493.
16. Aschoff: Pathol. Anat., 1922, **2**, 68.

* I wish to express my thanks to Dr. Edwards, Associate Professor of Physiology at Cornell University, for helpful suggestions on the physiological phases of this presentation.

THE NON-CALCULOUS GALL-BLADDER.*

BY RALPH R. MOOLTEN, A.B., M.D.,

ASSOCIATE IN SURGERY, NEW YORK POST-GRADUATE MEDICAL SCHOOL AND HOSPITAL.

(From the Surgical Service of Prof. Charles Gordon Heyd, New York Post-Graduate Hospital.)

THE last decade has witnessed a surprising amount of literature dealing with the pathology and symptomatology of the infected gall-bladder. It may be deduced from these contributions that it is the element of infection in the gall-bladder that accounts for the symptoms rather than the incidental or accidental presence of calculi. Although the presence of calculi may add certain mechanical elements, and be the exciting agent, as in hydrops, yet the disturbed physiology and aberration of gastrointestinal function is due to the changes that have taken place in the wall of the gall-bladder rather than the presence or absence of calculi within its cavity. If we could imagine the introduction of sterile pebbles into a normal non-infected gall-bladder in all probability the patient would be unaware of their presence, except in the event of some mechanical phenomenon, such as the production of an obstruction, or pain incidental to passage through a duct.

There are three factors necessary for the production of gall stones. These are: (1) Infection, (2) biliary stasis of some degree and (3) foreign material. Whether that foreign material is clumped bacteria or mucin is relatively unimportant. Significant for our present consideration is the fact that stones cannot be formed without an existing infection. We are further constrained to believe that cholelithiasis is only an incidental and often a late factor, because if the bacteria were of a certain degree of virulence the changes in the wall of the gall-bladder would be of such severity as not to produce stones. It is when the bacteria are of such lesser virulence as to produce only minor changes in the gall-bladder wall that the stones are formed. In the strawberry gall-bladder of Moynihan stones are absent. This is likewise true in many other forms of cholecystitis, where the infection has produced atrophic and fibrotic changes.

In contemplating conditions of the gall-bladder there are certain anatomical and physiological facts concerning this organ that are of more than mere academic interest. It is a noteworthy fact that, although the gall-bladder is a hollow viscus with its fundus lower than its outlet, it is incapable of completely emptying itself, because of the inadequacy of the muscular coat. However, it

* Read before the Surgical Conference of the New York Post-Graduate Hospital, January 17, 1924.

undergoes periodic rhythmic contracture at about the rate of 8 to ten times a minute. The secretory pressure of the bile as it descends from the liver down the common duct, combined with the contractile pressure of the gall-bladder, is not sufficient to open the sphincter of Oddi, in spite of the fact that the secretion and liberation of bile from the liver are continuous. It is only by an automatic inhibition of the neuromuscular apparatus of the sphincter of Oddi that the sphincter can be released. In consequence there is only periodic flow into the duodenum, although continuous flow from the liver.

The nature of the bile, as it leaves the liver, is different from the bile found in the common duct and in the gall-bladder. The latter is thicker, darker and of a higher specific gravity, and chemical examination reveals mucoid and albuminoid materials. Rous and McMaster have shown that within twenty-four hours the cystic duct concentrates the bile from two to four times, while the gall-bladder concentrates the bile ten times. Thus we see that although its function may be subserved by the common duct, the gall-bladder has a function, or at least a physiological potentiality, and in that respect differs from the appendix, a vestigial organ that has no function at all.

These various factors, taken together, make the biliary apparatus one of great physiological and neuromuscular complexity. Because of this interdependence of various anatomical units, we can readily understand how any disturbance in one will soon cause reflex symptomatology in another.

From the viewpoint of our present consideration, the anatomy of the biliary apparatus commands our interest at two points. The first is the ductal arrangement at the duodenal end; the second is the arrangement of the lymphatics of the region. The somewhat complicated developmental history of the pancreas explains the close relationship between the head of the pancreas, the duct of Wirsung and the common bile duct. Depending on the eccentricities of development, the relationship of these ducts to each other and to the duodenum will vary. Consequently, Letuelle describes four types of papillæ of Vater.¹ However, the experiments of Mann have shown that while it is barely possible for pancreatitis to be caused by the influx of bile into the pancreas, or by contact infection from one duct into the other, this does not occur except under the most unusual conditions. Infection usually invades the pancreas by way of the lymphatics from the gall-bladder.

"A study of the lymphatics of the liver and gall-bladder demonstrates that there is no barrier between the intra- and extrahepatic lymphatics, but that the liver lymphatics pass unobstructedly into the gall-bladder, and the lymphatics of the gall-bladder pass directly into the liver substance through the area of attachment of the gall-bladder to the liver. The lymphatic system would seem to be

the connecting link in infections of the gall-bladder, liver and pancreas."²

Having thus demonstrated the close anatomical relationship between the liver, gall-bladder and pancreas, we are in a position to understand how one can become infected by virtue of an infection existing in any other of them. If the gall-bladder is the primary focus the liver will soon suffer in consequence, and the pancreas, at the other end of the lymphatic chain, will become involved by very much the same process as the development of a lymphangitis. Deaver carries this corollary to a logical conclusion, and says that if removing a focus of infection will clear up a lymphadenitis, then removing a diseased gall-bladder will most certainly cure a pancreatitis.³

On the other hand, the liver by a hematogenous route (it is interposed between the portal and arterial circulation) may be the first to be involved, secondary to a lower abdominal focus, as, for example, a diseased appendix. Bearing in mind the lymphatic distribution, we can trace very readily a secondary cholecystitis. There is thereby instituted the inception of a vicious cycle; for should the infective process at the point of commencement cease to be active, the diseased gall-bladder will continue to involve the liver, producing hepatitis. Here we have the crux of a formidable pathological process. The splendid work of Heyd and MacNeal has shown hepatitis to be a very definite pathological and clinical entity, becoming progressively more of a menace with the duration of its existence.⁴ That it is productive of chronic digestive invalidism is clinically demonstrated by the fact that some cases of chronic cholecystitis are unimproved no matter what type of surgery may be done.

A significant factor in the diagnosis of non-calculous gall-bladder is the history of a gaseous indigestion, most often qualitative for certain fried or rich foods, without the occurrence of jaundice or of an attack of "gall-stone colic." In cases of longer duration the indigestion will often follow the ingestion of any food whatsoever, and therefore suggest the presence of a gastric ulcer. The picture of gall-bladder indigestion, however, lacks the almost mechanical precision with which events follow each other, which is ordinarily so characteristic of ulcer cases. The belching of large volumes of gas affords relief to the patient with gall-bladder disease, and after the gamut of carminatives has been run through, each being discarded as its worth has been spent because of too frequent use, it is not long before the sufferer learns to induce vomiting, to combat oppressive distention after eating. Many of these patients tell us that not infrequently they must excuse themselves from the dinner table, and after having successfully induced vomiting they are able to return and go through the rest of the meal in comparative comfort. We are all familiar with the old diagnostic axiom for gall-bladder disease, "fair, fat, forty and belching gas." Belching gas

remains the one most significant symptom, but with our better ability to interpret clinical symptoms we are recognizing a diseased gall-bladder to be the underlying pathology in an ever-increasing number of cases of indigestion, where the patient is not fat and not yet forty.

At laparotomy there are certain criteria in the absence of calculi that serve to indicate the presence or absence of pathology in a gall-bladder. Visualizing is necessary for a satisfactory examination of this organ; diagnosis based on palpation alone is apt to be fallacious; in any event, it is seriously open to question. Remembering the concentrating power of the gall-bladder, the presence of inspissated or thickened bile is in itself not indicative of the presence of infection. Ligamentous adhesions between the gall-bladder and the duodenum or the hepatic flexure of the colon occur with such frequency in cases where there is no other evidence of disease that their presence cannot indict the gall-bladder as pathological. What we consider as positive indications of disease are: (1) Loss of normal color. The normal color is olive green, with a bluish tinge. Exposure to air may cause changes in the color, therefore the gall-bladder should be inspected immediately on opening the abdomen, before other organs are explored. (2) A thickening of the walls is suggestive of infection, the degree of thickening being in direct ratio to the duration of disease. (3) The presence of pericholecystitis must be construed as indicative of disease within the walls of the gall-bladder; the evidence, however, must be present in addition to the so-called "normal cysticoduodenal and cysticocolonic ligaments" referred to above. (4) A deposit of saffron-colored fat over the fundus is not normal, and suggests mural infection. (5) A somewhat uncommon finding is a small red diverticulum on the fundus, and when present is indicative of sufficient pathology to warrant removal of the gall-bladder. (6) The single factor by itself most suggestive of disease is the presence of hyperplastic lymph nodes along the cystic duct and in the vicinity of Hartmann's pouch; when palpable, they are absolute indication of an infective process—either past or present. (7) On sectioning a diseased non-calculous gall-bladder, the mucous membrane is papillomatous in character, and often there is discernible the sparkle of tiny cholesterol crystals imbedded in the summit of the papillæ.

Conclusions. 1. Infection, not the presence of calculi, is the criterion of a surgical gall-bladder.

2. Hepatitis is almost an invariable, and pancreatitis a frequent, concomitant of biliary tract infection. Therefore, early surgery on an infective process is a wise procedure.

REFERENCES.

1. Letuelle and Nattan-Larrier: *Bull. Soc. anat. de Paris*, 1899, p. 987.
2. Heyd: *Long Island Med. Jour.*, January, 1923.
3. Deaver and Sweet: *Proc. Section on Surgery, Am. Jour. Med. Assn.*, 1921, p. 87; *Jour. Am. Med. Assn.*, 1921, 77, 194.
4. Heyd: *Surg. Clin. North America*, New York Number, 1923, p. 397.

PHENOLTETRACHLORPHTHALEIN IN THE STUDY OF LIVER FUNCTION.

BY W. W. BOARDMAN, M.D.,

AND

G. D. SCHOONMAKER, M.D.,

SAN FRANCISCO, CALIF.

(From the Gastroenterological Clinic, Stanford University Medical School.)

THE development of a satisfactory liver function test is greatly to be desired. Numerous tests have been proposed, based either on a study of one of the specialized functions of the liver or upon the excretion of some foreign dye.

There is no object in reviewing at this time the first group of tests further than to recall that they have been disappointing and have failed of general adoption.

Of the second group we shall consider only phenoltetrachlorophthalein which has since its introduction held the promise of a satisfactory test, provided the method could be sufficiently simplified. This seems to have been accomplished, and it now remains to accumulate data for the purpose of standardizing the technic and of properly evaluating the findings. To this end a brief review of the methods and findings so far reported follows:

Review of Literature. The original technic, as proposed by Rowntree,¹ required the collection of total stools over a forty-eight-hour period, and the extraction and estimation of the dye present in this material. With this technic there was no unanimity of opinion regarding the value of the test, and owing to the technical difficulties it was soon discarded.

However, in 1916, MacNeil² revived the test, using the duodenal tube to collect the dye containing bile after the intravenous injection of 40 mg. of phenoltetrachlorophthalein. This enabled him to observe the appearance time of the dye in the bile, as well as to estimate the amount excreted in a two-hour period, and did away with the necessity of collecting and working with forty-eight-hour stools. He had difficulty at times, however, in establishing a satisfactory flow of bile. With this technic he found in 7 presumably normal cases an appearance time of from twelve to twenty-five minutes (Table I) and a two-hour output of from a trace to 10 per cent. In 5 cases of atrophic cirrhosis and 1 of extensive carcinomatosis of the liver the appearance time was increased, varying from twenty-eight to forty-five minutes, but the two-hour output was practically the same as in the normal controls. From these observations he concluded that the quantitative estimation of the

two-hour excretion is of little value, but that the appearance time is rather decidedly delayed in certain pathological conditions of the liver.

TABLE I.—APPEARANCE TIMES AND AMOUNT OF PHENOLTETRACHLORPHTHALEIN USED BY PREVIOUS OBSERVERS.

	MacNeil.	Aaron.	Williamson.	Higgins.	Friedenwald.	Piersol.	Boardman.
	7 cases.	16 cases.	15 cases.	5 cases.	95 cases.	15 cases.	10 cases.
Minimal and maximal	18	..	5.00	7
Initial appearance, times	21	..	11.00	10½
Minimal and maximal	12	14	16	55	..	8.75	9½
Maximum appearance, times . .	21	20	24	105	23	15.00	13
Amount of dye injected, mg. . .	40	50	50	50	75	150	150

MacNeil's report apparently aroused little interest, for it was not until 1921 that further reports appeared. In this year Max Kahn,³ in a brief note on the Lyon-Meltzer method, stated that traces of phenoltetrachlorpht halein appeared in the bile of the duodenal content within twenty minutes of the time of injection. The amount of the dye injected is, however, not stated.

Later in the same year Aaron, Beck and Schneider⁴ simplified the technic by first describing a method of preparing a stable solution of the dye, thus obviating the necessity of making a fresh solution for each test and second stated that by the administration of 500 cc of cool water by mouth after the tube had reached the duodenum a continuous flow of from 60 to 80 drops of bile-stained material a minute could be established and maintained for from one-half to three-quarters of an hour. They injected 50 mg. of the dye, and noted the initial appearance time and maximum appearance time of the dye in the drip from the duodenal tube. These times are determined by allowing the bile to drip into white porcelain dishes containing 40 per cent solution of NaOH, the initial appearance of the dye being indicated by a faint purplish ring at the point of contact of the bile and the alkali, and the maximum appearance by the point at which no further intensification of the color occurs with succeeding drops.

With this technic they found in 16 cases with no evidence of liver disease a maximum appearance time of from fourteen to twenty minutes (Table I), whereas in 7 cases with evidence of dis-

turbed liver function they found a maximum appearance time definitely prolonged. From their studies they conclude that the quantitative estimation of the dye excreted in a given time is of no value, because of the factor of leakage into the lower bowel, that a maximum appearance time of more than twenty minutes is suspicious of liver involvement, and that the test may be of great value in following the course of liver diseases.

Piersol and Bockus,⁵ in 1923, followed in general the technic of Aaron, but used 150 mg. of the dye instead of 50, noted the time of initial appearance of the dye, the time of maximum appearance and estimated the total two-hour output. They report 50 cases, 15 presumably normal and 35 suffering from various pathological conditions, and divide them into four groups solely on the basis of the quantity of dye excreted in the two hours: Thus, in Group I are the 15 presumably normal cases, showing a two-hour elimination of from 19 to 27 mg. of the dye, an initial appearance time of from five to eleven minutes and a maximum appearance time of 8.75 to 15 minutes (Table I). In Group II 17 cases are presented with a two-hour excretion of from 10 to 19 mg., an initial appearance time varying from seven to twenty-five minutes and a maximum appearance time varying from ten to twenty-six minutes. In Group III there are 8 cases with a two-hour output of from 5 to 10 mg., but here again the initial appearance time varies from seven to twelve minutes, and the maximum appearance time varies from eleven to twenty-four and a half minutes, and finally in Group IV there are 10 cases with a two-hour excretion of less than 5 mg., with an initial appearance time of from eight to twenty-four and a half minutes and a maximum appearance time of from fourteen to twenty-nine and a half minutes.

From these findings they conclude that in a general way a delay in the appearance time is proportionate to a decrease in the two-hour output, and that the quantitative estimation of the two-hour output is of greater importance than the appearance time, although both should be considered. It is their impression that the two-hour output will show lesser grades of functional disturbance than will the initial and maximum appearance times.

Higgins,⁶ using 50 mg. of the dye, noted the initial and maximum appearance times, also the disappearance time, or the time at which the dye ceased to appear in the bile, and finally estimated the total amount of dye excreted. He concludes from a study of 5 presumably normal cases that the initial appearance time varies from eighteen to twenty-one minutes, and the maximum from fifty-five to one hundred and five minutes (Table I). He also found the disappearance time to vary from ninety to one hundred and thirty-five minutes and the total output to vary from 40 to 48 per cent. In 16 pathological cases he found delay in the appearance times and decrease in the total output in those in whom liver

disturbance might be suspected, and concludes that the method is of value in the study of liver conditions.

Friedenwald,⁷ later, in 1923, using 75 mg. of the dye, reports on 93 cases, and concludes that the normal average initial appearance time is thirteen and four-fifths minutes and that a delay of more than twenty-three minutes indicates hepatic disease or mechanical obstruction (Table I).

Dakin and Graham,⁸ in a combined clinical and experimental study, were unfavorably impressed, but especially with the quantitative estimation, because of the various factors which seemed to prevent a complete collection of the liver bile by means of the duodenal tube.

Williams⁹ studied 20 pregnant women, using 50 mg. of the dye, and found that the normal maximum appearance time varied from sixteen to twenty-four minutes (Table I). In 5 showing albuminuria 3 gave normal reactions and 2 a delayed appearance time. He was unable to draw any conclusions from this study.

While these reports dealing with the duodenal-tube method were appearing, Rosenthal,¹⁰ recognizing some of the defects of this technic, developed his method. His experimental work was based on the theory that as the liver is practically the only organ involved in the elimination of phenoltetrachlorphthalein, and as the dye only appears in the urine where there is evidence of decreased output by the liver, it is probable that there is retention of the dye in the blood when liver function is impaired. With this idea in mind, he studied a series of normal dogs and found that after the intravenous injection of 5 mg. of phenoltetrachlorphthalein per kilo of body weight there was an immediate rise of the dye in the plasma to approximately 10 per cent, with a rapid fall to only a trace or complete disappearance within fifteen minutes. When the liver was experimentally damaged there was an immediate rise to from 15 to 30 or more per cent and the values remained elevated for a prolonged period, 11 per cent having been recovered almost two hours after injection. There was evidence that the curves of retention paralleled the degree of impairment of liver function.

These facts having been established, he applied the test clinically,¹¹ injecting 5 mg. per kilo dissolved in 25 to 30 cc of physiological sodium chloride solution into a superficial vein of one arm after first collecting about 8 cc of blood. Fifteen and sixty minutes after this injection 2 to 4 cc of blood was withdrawn from the other arm, and allowed to clot. The plasma was pipetted off and put into separate small test-tubes of uniform size and 1 drop of 5 per cent NaOH added to each tube. Phenoltetrachlorphthalein, 10 mg., was now added to 100 cc of water, this strength representing approximately the concentration that would be reached if all the injected dye remained in the plasma. With the plasma obtained before the injection of the dye, a series of standards was prepared in small

test-tubes of similar size, ranging from 25 to 3 per cent. The plasma in which the amount of dye was to be determined was matched with these standards.

Using this technic, he examined 10 normal cases and 10 cases of extrahepatic disease, and in these 20 cases he found from 2 to 6 per cent of the dye present at the fifteen-minute interval; practically complete absence at the sixty-minute interval. In 5 cases of carcinoma of the liver, 3 of cirrhosis and 9 of miscellaneous liver diseases, there was a more or less marked retention of the dye at the fifteen-minute and one-hour interval, the degree of retention apparently giving an index of the functional disturbance of the liver. He encountered no general reactions, but did have frequent induration of the vein at the site of injection and in 2 cases localized thrombosis, which persisted for several days. In the 20 normal and control cases no dye appeared in the urine, whereas in the pathological cases all but 4 showed dye in the urine, but not in proportion to the concentration in the blood.

From this work Rosenthal concluded that this method of testing liver function depends on the ability of the liver to remove the dye from the blood stream, that it is not difficult or time-consuming, that there is retention of the dye in the plasma in cases of hepatic disease and that the results are quantitative and probably give an index of the functional capacity of the liver.

In 1923 Rosenfield and Schneider,¹² practically following Rosenthal's technic, studied 6 normal pregnant women and 7 with neurotic or toxic vomiting, and confirmed Rosenthal's conclusions both as to the rate of disappearance of the dye in normal cases and to the value of the test in studying hepatic disease.

From this review it is evident that practically all investigators who have so far reported are convinced of the value of phenoltetrachlorpht halein in the study of liver function. However, considerable work remains to be done and several points settled before the test can be generally adopted. Thus, in the duodenal-tube method a standard amount of the dye must be employed, the limits of normal variation in the appearance times must be defined and the value or lack of value of the quantitative estimation of the dye output determined. Again the relative merits and demerits of the Rosenthal and duodenal tube methods must be established and the indications or contraindications for the use of one or the other method defined, and finally there must be accumulated a mass of carefully studied clinical material controlled by pathological examinations before the real value of the test can be established.

Clinical Studies. In an effort to clarify some of these points we undertook the following study of normal and pathological cases, using in the majority both the Rosenthal and duodenal-tube methods. In the former we followed the original technic without essential modification; in the duodenal-tube method we also followed the usual technic, using 150 mg. of the dye, as suggested by Piersol.

We made no quantitative estimations of the output of the dye by the duodenal-tube method, as we convinced ourselves that it was impossible to collect uniformly by the duodenal tube all the bile excreted by the liver over any given period.

There are two factors which make this impossible. The first is the indeterminate amount of bile that may find its way into the gall-bladder during the period of the test and thus escape collection by the tube. We have repeatedly demonstrated upon dogs and operative cases that large amounts of the dye are present in the gall-bladder bile from fifteen minutes to several hours after injection. It may be objected that if we had had the tube in the duodenum and the drip established no freshly secreted liver bile would have entered the gall-bladder, but that it would all have been discharged into the duodenum. This does not seem probable and certainly cannot be accepted without ample proof. However, even disregarding the first factor, the second, that of leakage into the small bowel, is sufficient. This leakage we have demonstrated by recovering large amounts of the dye in the stools following a routine test in which, however, the drainage was continued beyond the time of disappearance of the dye from the bile.

Piersol and Bockus, however, concluded that the quantitative estimation of the two-hour output was a more accurate indication of slight functional disturbances than the appearance time. Yet if we study their charts it seems apparent that they have accepted without confirmatory proof that the quantitative estimation is of prime importance. Thus they have divided their cases into four groups solely on the basis of the two-hour output. On this basis 35 cases fall into the three groups apparently having some disturbance of liver function, but of these 35 cases 17, or 48.5 per cent, have an initial appearance time falling within their limit of normal, and of these 17 cases 13, or 37.1 per cent, have also a maximum appearance time within their limits of normal. On the other hand, they fail to present any clinical or pathological evidence of liver disease in these cases with normal appearance times. We, therefore, cannot agree with Piersol and Bockus or with Higgins as to the value of the quantitative estimation of the dye, but do agree with Friedenwald, Aaron, Graham and MacNeil that it is useless as a functional test.

Using 150 mg. of the dye, we found (Table II) by the duodenal-tube method in 10 presumably normal cases an initial appearance time of from nine and a half to thirteen minutes. These figures agree very closely with those reported by Piersol, who used the same amount of dye, and are somewhat lower than those of the other observers who used smaller amounts of the dye. Higgins' figures alone are not in keeping with the general average and cannot be explained.

TABLE II.—RESULTS OF THE ROSENTHAL AND DUODENAL-TUBE METHODS IN TEN APPARENTLY NORMAL CASES.

Case No.	Rosenthal.		Duodenal tube.	
	Per cent at 15 minutes.	Per cent at 40 minutes.	Initial appearance time.	Maximum appearance time.
I	5	0	7	9½
II	5	0	7½	10
III	5	0	8	11
IV	5	0	8	11
V	6	0	8½	10
VI	5	0	8½	11
VII	6	0	9	10
VIII	6	0	9	12
IX	5	0	10	12
X	8	0	10½	13

With the Rosenthal method these same 10 apparently normal cases gave fifteen-minute values of from 5 to 6 per cent, with the exception of 1 case, which showed 8 per cent (Table II). At the forty-minute period after injection the dye was absent from the serum in all. These findings agree with Rosenthal's, except for the 1 case showing 8 per cent at fifteen minutes, and it is of interest that this same case gave the highest values for the initial and maximum appearance times of the series.

It is, therefore, evident that our findings agree with those of Rosenthal and Piersol, and especially that the two tests seem to show an absolute parallelism.

TABLE III.—RESULTS OF THE ROSENTHAL AND DUODENAL-TUBE METHODS IN TWENTY-TWO CASES OF CHRONIC CHOLECYSTITIS.

Case No.	Rosenthal.		Duodenal tube.	
	Per cent at 15 minutes.	Per cent at 40 minutes.	Initial appearance time.	Maximum appearance time.
I	4	0	7	11
II	6	4	8	10½
III	8	0	8	11
IV	8	0	9	12½
V	6	0	9½	11
VI	5	0	9½	11
VII	9½	12
VIII	8	0	9	14
IX	9	14
X	6	0	10	12½
XI	6	0	10	14
XII	8	2	10	15
XIII	6	0	10½	13
XIV	8	0	10½	16
XV	9	0	11	13
XVI	9	2	11	16
XVII	10	2	12	16½
XVIII	8	0	12½	15
XIX	9	2	13	16
XX	10	4	13	18
XXI	10	4	14	18
XXII	10	4	15½	17½

Table III shows the results of the tests in a series of 22 cases of chronic cholecystitis in which more or less functional disturbance was to be anticipated. The most striking feature of this study is the almost absolute parallelism of the two tests, Case II being the only exception and remaining as yet unexplained.

In 10 cases of definite liver disease the same parallelism between the findings by the two tests and the apparent ability of either test to demonstrate disturbed liver function is evident in Table IV.

TABLE IV.—RESULTS OF THE ROSENTHAL AND DUODENAL-TUBE METHODS IN TEN CASES OF DEFINITE LIVER DISEASE.

Case No.	Clinical diagnosis.	Rosenthal.		Duodenal tube.	
		Per cent at 15 minutes.	Per cent at 40 minutes.	Initial appearance time.	Maximum appearance time.
I*	Cholecystectomy five years before; recurring attacks of pain and jaundice since	10	6	8½	11
II†	Acute hepatitis	15	2	9	14
III	Cholecystectomy	8	0	12	15
IV‡	Cirrhosis, cardiorenal	15	10	12½	16
V	Cirrhosis, syphilis	16	12	15	25
VI	Hanot's cirrhosis	9	9	15½	31
VII	Hepatitis, acute	12	12	16½	18
VIII	Colangitis	17½	27
IX	Cirrhosis	16	14	19	28
X	Hepatitis	20	16	24	28

* Rosenthal test performed a week later than the duodenal tube test, and was followed in a few days by an attack of pain with jaundice.

† Rapidly clearing acute hepatitis. Duodenal tube test done twenty-four hours after the Rosenthal.

‡ Rosenthal test done day before duodenal tube test.

In Table V are tabulated the findings in a group of miscellaneous pathological conditions apparently free from liver involvement. Here again is shown the close parallelism between the two tests.

TABLE V.—RESULTS OF THE TWO TESTS IN FIVE PATHOLOGICAL CASES WITHOUT EVIDENT LIVER INVOLVEMENT.

Case No.	Clinical diagnosis.	Rosenthal.		Duodenal tube.	
		Per cent at 15 minutes.	Per cent at 40 minutes.	Initial appearance time.	Maximum appearance time.
I	Ileocolitis	5	0	7	10
II	Healed duodenal ulcer	4	0	8	10
III	Hyperacidity	6	0	8½	11
IV	Duodenal ulcer	5	0	8½	10
V	Cardiorenal anemia	5	5	10½	15

Conclusions. 1. In phenoltetrachlorpht halein we have a valuable means of studying the functional activity of the liver.

2. The findings by the duodenal-tube method and the Rosenthal method are apparently of equal value and significance.

3. Therefore the choice of method ordinarily rests with the individual preference of the investigator, except in cases of common duct obstruction, or when for one reason or another the passage of the tube is contraindicated or impossible. Our own preference is for the duodenal-tube method whenever possible, because of the natural objection on the part of the patient to the injection of large amounts of highly colored material intravenously and because of the danger of induration and thrombosis with these large injections which are necessary in the Rosenthal method.

4. With the duodenal-tube method we would recommend the adoption of the 50-mg. dose as the standard, because there is no apparent advantage in the larger doses.

5. Because of the impossibility of collecting all the bile excreted over a given period quantitative estimations by the duodenal-tube method are of no value.

6. With 150 mg. of the dye an initial appearance time of eleven minutes or over, and a maximum appearance time of fourteen minutes or over, would seem to indicate liver disturbance. In normal cases the time between the initial and maximum appearance of the dye rarely exceeds three minutes. In pathological cases this time is frequently but not uniformly increased. It is our impression that the maximum appearance time may occasionally be influenced by the factor of dilution by the gastric contents (the water given the patient to drink) and, therefore, be less reliable than the initial appearance time.

BIBLIOGRAPHY.

1. Rowntree, Hurwitz and Bloomfield: Bull. Johns Hopkins Hosp., 1913, 24, 327.
2. MacNeil: Jour. Lab. and Clin. Med., 1915, 16, 1.
3. Max: Jour. Am. Med. Assn., 1921, 77, 41.
4. Aaron, Beck and Schneider: Jour. Am. Med. Assn., 1921, 77, 1631.
5. Piersol and Bockus: Arch. Int. Med., 1923, 31, 623.
6. Higgins: Ann. Clin. Med., 1923, 11, 30.
7. Friedenwald and Gantt: AM. JOUR. MED. SCI., 1923, 166, 519.
8. Deakin and Graham: Surg., Gynec. and Obst., 1923, 36, 348.
9. Williams: Am. Jour. Obst. and Gynec., 1922, 4, 26.
10. Rosenthal: Jour. Pharmacol., 1922, 19, 385.
11. Rosenthal: Jour. Am. Med. Assn., 1922, 79, 2151.
12. Rosenfield and Schneider: Jour. Am. Med. Assn., 1923, 80, 743.

OBSERVATIONS ON THE TREATMENT OF PRIMARY AND SECONDARY SYPHILIS.*

BY B. A. THOMAS, A.M., M.D.,

PROFESSOR OF UROLOGY, UNIVERSITY OF PENNSYLVANIA; GENITO-URINARY SURGEON
TO THE PRESBYTERIAN HOSPITAL, PHILADELPHIA.

THE old dictum that the most successful practitioner of medicine is he who most successfully treats syphilis was never truer than today. Fourteen years of empiricism with the arsenicals has at least taught us the folly of reliance only on this chemical in the treatment of lues, also the archaism of the belief that syphilis can be satisfactorily treated by mercury alone. Certain outstanding facts have become apparent: (1) The necessity of early diagnosis and the urgency of intensive, efficient treatment in order to cure, and the irreparable evil of single or small dosage and desultory treatment. (2) The superiority of maximum to fractional dosage of salvarsan and neosalvarsan or their substitutes as a sheet-anchor in therapy. (3) The increased incidence of arsenical reactions. (4) The decreased effect on the Wassermann and other serological reactions and an increment in the number of "Wassermann-fast" cases. (5) The apparent dissatisfaction with the arsenicals, as evidenced by resort to a galaxy of other drugs, notably, mercury, bismuth, silver- and sulphur-arsphenamin. (6) The advisability of synchronous or supplemental treatment with mercury and other drugs. (7) The necessity of efficient "follow-up" on blood and spinal fluid.

In this connection I cannot refrain from directing attention to former reports in 1916¹ by myself on the treatment of syphilis.² It seems to be a fact that the results then obtained have not been surpassed and probably not equalled by the substitutes of old salvarsan and neosalvarsan or by any modifications of the technic employed at that time, which followed implicitly the dicta and precautions laid down by Ehrlich. At that time it was our experience and I think generally conceded that salvarsan was more effective than neosalvarsan, particularly so far as the Wassermann reaction was concerned, which, after all, is an indispensable criterion in the successful treatment of syphilis. Then it was observed that if patients in the primary and secondary stages of the disease have a sufficient number of injections of salvarsan or neosalvarsan to secure a negative Wassermann, a possibility in 95.2 per cent of cases, it remained negative in the vast majority of patients for one to three years and in some cases for five and a half years, even though no mercury was used. In a few patients with chancres that we have been able to follow, the blood and spinal fluid Wassermanns have remained negative in the absence of any other treatment for twelve

* Read before the Philadelphia County Medical Society, May 14, 1924.

years. In reviewing these results and contrasting them with the experience of today, using modified technics and the present-day arsenicals and other drugs substituted for 606 and 914, we are struck with the inferiority of results, clinically and serologically, the greater number of "Wassermann-fast" cases, the increase in severe reactions, notably dermatitis and the increased necessity for supplementary mercurial therapy. What is the explanation? Either the substitutes for salvarsan and neosalvarsan are not so potent as the originals or the technic of administration today is not so good. I believe both are true, and the sooner we return to the original instructions for preparation and injection, specified by Ehrlich and his co-workers striving for Ehrlich's ideal "*therapia sterilisans magna*," the better it will be. We must look forward to an improved preparation, more potent as a spirochetocide and less toxic, whereby more intensive and larger dosage can be employed, and fractional or small dosage of the present day preparations may be obviated.

I am confident that a large proportion of the reactions following the intravenous administration of the arsenicals is due to erroneous present-day technic of administration, and believe that employment of solutions isotonic with the blood, freshly and properly distilled sterile water of the proper temperature for dissolving and diluting the drug, and immediate slower injections and the elimination of mercury synchronously with the administration of the arsenicals, will materially reduce the number of serious reactions. Doubtless some are due to individual idiosyncrasies. In our experience the percentage of reactions from neosalvarsan exceeded that from salvarsan, but were not so severe; and in neither case were they comparable with the reactions obtained from the present-day substitutes. In recent years reactions have been minimized by resort to fractional doses more frequently administered, but likewise with diminished therapeutic effect.

Nitritoid crises, neurorelapses and jaundice due to an injury to the liver by the toxins of syphilis, have decreased in frequency, but the skin reactions have increased materially. Insufficient attention is given to gauging the dose proportionally to the body weight. Too much stress cannot be laid on the observance of the contraindications; nephritis, not due to lues, other concurrent infections and jaundice or skin reactions incident to previous injections. The production of or the contraindication offered by nephritis should be easily avoided by routine urinalysis before the first injection and the morning after each injection of the arsenicals.

The administration and value of epinephrin for the control of nitritoid crises is too well known for further comment. Sodium thiosulphate intravenously, at first daily and later on alternate days, in doses ranging from 5 to 25 grains, seems to possess definite antidotal properties and promises to be of exceptional merit in arsphenamin dermatitis.

The paramount requisition for cure in the treatment of syphilis is early diagnosis. If that diagnosis can be made in the primary stage before the advent of a positive Wassermann reaction, and that can and should be done in about 90 per cent of patients, the number of incurable cases should be very small. On the contrary, if the diagnosis be delayed until after the serological test becomes positive, the case must be regarded and treated as one of secondary syphilis, and the prognosis as to ultimate cure becomes at once and for all time, far less hopeful. Granted that, although it is possible in the majority of patients, to diagnose primary and secondary syphilis, clinically, no medical audience today needs to be reminded of the indispensable utility of the dark-field microscope for the only sane and safe management of doubtful sores or the examination of aspirated fluid from the regional lymph nodes in the event of negative findings from suspicious ulcers, or the Wassermann reaction, not so much from the diagnostic as from the prognostic and treatment standpoint.

Over ten years ago we pointed out³ "that there should be some means of coöperation of Wassermann workers for standardization and uniformity of methods, to be adhered to as long as they are justified by clinical results, with the acceptance from time to time of such advances in technic as may be approved. In this way only will the serological syphilis reaction retain the confidence that its intrinsic value merits." Apropos of the discredit which at times has attached to this most valuable test of syphilis, it should be impressed today that the incidence of false positive Wassermann reactions with cholesterinized antigens has been reduced or removed by Kolmer's new antigen, and his persevering researches in this work is an important step in the right direction for the standardization of the serological diagnosis of syphilis.

Finally, I should like to enter a vigorous plea against the use of the term "Wassermann" in the presence of patients. It is one of the most deplorable mistakes in modern medical practice. There is no more reason for the patient to know why he is having his blood tested or the result thereof, than there is to be informed of his routine blood count, biochemical test or urinalysis. Some, as the result of persistently positive Wassermanns, commit suicide, go crazy or become physical, mental and moral wrecks. Others, after a short course of treatment and a negative blood test, are prone to regard the decision too lightly, assume they are cured, neglect further necessary follow-up treatment with the inevitable result of latent tertiary or neurosyphilis.

The prophylactic, or what our ecclesiastical brethren are wont to call the early, treatment of lues, in addition to soap and water cleansing and bichloride or mercury washes, consists mainly in the use of the introduction of 33½ per cent calomel ointment into the urethra and smeared over the genitalia within an hour of exposure.

The value decreases practically to *nil* in eight hours. In the female, owing to the difficulty of carrying out the calomel ointment applications, three intravenous injections of salvarsan should be given. This should also be done in the male if the routine prophylaxis has not been applied in the first hour.

Irrespective of rules, methods and drugs, each case of syphilis is a study unto itself as to the best and most efficient method of treatment. Here as in every other phase of medicine the patient as well as his disease must be intelligently treated. My procedure in primary and secondary syphilis, as well as it may be defined is as follows: The Wassermann reaction is the great therapeutic divide. Its importance lies not so much in the field of diagnosis as in the realm of prognosis and treatment. It is utterly illogical and nonsensical to treat a patient with a chancre and a negative Wassermann that does not become positive under treatment, as vigorously and as long, as another patient with a positive Wassermann, irrespective of degree. Therefore, from the standpoint of treatment, we divide our patients in the primary and secondary stages of lues into two groups, those with negative, that is, in the early primary stage, and those with positive serological reactions, that is, the late primary and secondary stages.

In the first group, with efficient treatment, the prognosis is very good and cure can be expected in the vast majority of cases. This is the time to begin the treatment of syphilis, when it may be aborted and the patient can usually be assured an absolute cure. Three to 6 full-sized intravenous injections of salvarsan, neosalvarsan or their substitutes at weekly intervals are administered, the first given immediately on the day the patient first presents himself, for I regard the syphilitic in this stage of the disease just as much an emergency proposition from the standpoint of treatment and cure as the diphtheritic so far as antitoxin is concerned. Before each injection the blood should be taken to detect the possible advent of a positive Wassermann reaction, which occurrence will markedly influence subsequent treatment. I have never observed the development of syphilis in a Wassermann-negative patient in this group when old salvarsan or neosalvarsan was used employing as few as 3 injections, even without mercury. I have followed a few of these cases for twelve years, during which time they have never exhibited clinical evidence of syphilis and today present negative bloods and spinal fluids. I am not at all convinced that supplemental mercurial treatment is demanded in this group.

Excision of the chancre is not necessary, but may be done if located on the prepuce or if complicated by phimosis. The application of calomel or one of the arsenicals to the chancre itself, though of little value, will relieve the mind of the patient.

The second group, irrespective of whether the patient is in the late primary or secondary stage of the disease, furnishes the real test of our knowledge of the treatment of syphilis. The consensus

of opinion of the leading syphilographers at present is that this Wassermann-positive group should be treated continuously for one to two years even though the blood test is rendered negative in a few weeks. With this verdict I am heartily in accord and feel that too much reliance in the past has been placed on the production of a negative Wassermann from a few arsphenamin injections, administered in a desultory manner, and supplemented or not by a short or obviously inadequate course of mercury. In this group, not less than 6 full-sized doses (0.1 gm. per 30 pounds body weight) of salvarsan or neosalvarsan should be given at weekly intervals, in the absence of contraindication. Two to three weeks thereafter, the Wassermann should be determined, but irrespective of that finding, a second series of not less than 6 injections of the arsenicals should be administered, followed by another serological blood test. Should this be negative as invariably will be the case, an examination of the spinal fluid by Wassermann, globulin, cell count and colloidal-gold tests, should be advised. This is the stage when neurosyphilis frequently begins, hence the necessity for spinal fluid investigation, since in untreated and badly treated cases, 25 per cent of fluids will show abnormalities, and even in properly treated primary and secondary syphilis, lymphocytosis, positive globulin and rarely a positive Wassermann and gold curve will be found in about 15 per cent of patients. In the event of abnormalities in the spinal fluid a third or additional series of intravenous injections should be given until the spinal fluid as well as the blood is rendered negative and thereafter another supplementary series. During this time of intensive intravenous therapy by the arsenicals, I have not found it necessary or advisable to employ mercury in any form. At this juncture, however, intensive mercurial treatment should be begun, employing the protiodide pill, clean inunctions or hypodermics of bichloridol, salicylate or gray oil or intravenous injections of cyanide of mercury. Mercurial therapy is persisted in continuously until physiological intolerance is manifest, when the treatment is suspended temporarily and then resumed and held at one-half the former dosage and given in series with periods of rest for two years. The blood examination should be repeated at three to six month intervals the first and second years of treatment and the spinal fluid yearly, in the event of negative blood findings, throughout the patient's life. In the event of blood and spinal fluid abnormalities, intensive treatment with the arsenicals should be resumed. The iodides, so important in tertiary and neurosyphilis, seem to be superfluous in the primary and secondary stages of the disease.

It has long been apparent to me that small or fractional doses of arsphenamin and neoarsphenamin are a mistake for the most efficient treatment of lues, and I prophesied during the recent war that the current practice of small dosage to avoid reactions and keep the men in the firing line was fraught with future peril. Some vindication of the truth of this assertion has already been observed.

It is bound to come. We have heard much of "Wassermann-fast" reactions, but I am happy to state that with the procedure of treatment above detailed I have observed only 2 or 3 cases in many hundreds of patients. I have the conviction that were fractional dosage eliminated from therapy and other drugs withheld until salvarsan or neosalvarsan had accomplished their fullest benefit, administered according to the explicit directions of Ehrlich, fewer severe reactions, fewer immune treponemata pallida and greater and more enduring therapeutic results would be observed.

We have all been surprised and disgusted, if not impressed, in recent years by the great plethora of drugs of the arsenic, mercury, bismuth, silver, antimony, iodine and zinc combinations and brands. A conservative estimate of those marketed numbers not less than sixty. Either much dissatisfaction has been experienced with former antisyphilitic agents or over zealous individuals, laboratories and pharmaceutical firms are crazed with unwarranted impulses to produce something novel for the sake of personal distinction or notoriety or simply for commercial gain. In any event, the pharmaceutical deluge is regrettable, has resulted in much unwarranted experimentation with human life and produced not a few syphilitic derelicts. The most notable of these newer drugs are bismuth, of which potassium and sodium tartrobismuthate, an insoluble salt, is probably the best. It is slower in action than the arsenicals, both clinically and serologically, therefore inferior. It may be on an equal therapeutic footing with mercury, but its toxic complications are more serious than those of mercury. Silver- and neosilver-arsphenamin have received considerable favor in the treatment of neurosyphilis. Compared with the old arsenicals it has the additional disadvantage that argyria has been reported from its use. Sulpharsphenamin or arsenol, less irritating intramuscularly than the original arsphenamins, has not measured up to the fondest hopes of its progenitors. Briefly stated, the therapeutic efficiency of those drugs compared with old salvarsan or neosalvarsan has been disappointing, and their indications for employment exist solely when the former should not be used, namely: Idiosyncrasies against arsenic or mercury, in "Wassermann-fast" cases, possibly in neurosyphilis and in patients where intravenous therapy is inadvisable or impossible.

When shall the patient be permitted to marry and procreate? So much depends upon the duration of infection and condition of the blood at the time treatment was begun, the intensity, character, duration and time elapsed since suspension of that treatment, that each case must be determined on its own merits. Generally speaking, if an opinion must be given, it would be that marriage may be permitted after two years of adequate treatment and an additional year following treatment in which the patient is clinically free of any evidence of lues and the blood and spinal fluid show no abnormalities, although marriage may not be interdicted in a blood

"Wassermann-fast" reaction if the spinal fluid is normal. Procreation should not be sanctioned for two years after marriage and then only in the event of normal blood, spinal fluid and clinical evidence. If the patient be a woman, the restrictions should be more severe. Two years must be allowed to elapse following two years of vigorous and efficient treatment and should pregnancy occur, adequate antisyphilitic treatment must be carried out during that and all subsequent gestations. Antiluetic treatment of the child, even in the absence of clinical signs, is not inadvisable. Just as it is an axiom in latent, tertiary and neurosyphilis, so it is doubtless true that the wise syphilologist will advise his patients in the primary and secondary stage of the disease, at any time exhibiting a positive serological test, to undergo a course of treatment once or twice a year throughout their lives.

The social and economic burden upon the community and taxpayer, so far as human wreckage is concerned incident to syphilitic miscreants and improperly treated syphilis is appalling and difficult of comprehension. In 1916,¹ we pointed out in hospital out-patient services that 44 per cent of 557 syphilitics utterly disregarded or ignored their disease, at least primarily, that less than 19 per cent of those patients solicited by personal letters returned to the dispensary and that two-thirds of these were utterly indifferent or refused treatment, stating they "did not care." Accordingly, we concluded at that time that "in view of the fact that less than 12 per cent of our hospital syphilitics return for treatment until discharged cured, a problem is presented which urgently demands the coöperation of our civil authorities and health boards for the necessary control and treatment of this disease, not, however, to be realized until all hospitals receiving State aid are compelled to maintain evening dispensaries with paid attendants for the proper treatment and admission, when necessary, of venereal patients." Happily three years later, through the efforts of Dr. Edward Martin, the State Department of Health, through its advisory Board, acting apparently on these suggestions, passed regulations, defining methods by which quarantine could be applied. Since that time 736 lapsed treatment cases were reported in Philadelphia of whom 405 were reclaimed; three premises were placarded and police quarantined until removal to the Philadelphia General Hospital. In the entire Commonwealth approximately 7000 patients have been quarantined. This is surely a step in the right direction for our economic welfare.

BIBLIOGRAPHY.

1. Thomas: "Modern Diagnosis and Results Clinically, Serologically and Sociologically of Syphilis Treated with Salvarsan, etc." *Pa. Med. Jour.* 1917, 20, 254.
2. Thomas and Barnett: "The Modern Diagnosis and Treatment of Syphilis—An Analysis of 557 Cases," *New York Med. Jour.*, 1917, 105, 879.
3. Thomas and Ivy: "Observations on the Wassermann Reaction," *AM. JOUR. MED. SCI.*, 1914, 148, 55.

THE PATHOLOGY OF TUBERCULOSIS IN INFANCY, WITH CLINICAL ILLUSTRATIONS.

By FREDERIC H. BARTLETT, M.D.,

AND

MARTHA WOLLSTEIN, M.D.,

NEW YORK.

(From the Babies' Hospital, New York City.)

TUBERCULOSIS occurring in infancy is even more apt than in older subjects to affect every tissue and organ of the body. The period covered by the term "infancy" includes the first two years of life, but in this paper especial emphasis will be placed on manifestations in the first year. After two years of age, tuberculosis in its pathology, its symptoms and its physical signs enters upon a transitional period leading to the adult type.

The resistance of the infant to infection with the tubercle bacillus is low, and, as a rule, the younger the infant the more generalized does the infection become. The gross and microscopical anatomy of the acute lesions found in young children differ in no essential from those of the acute lesions in older patients. The real difference between tuberculosis in infancy and in later life lies in the fact that practically all the lesions seen at autopsy in children under two years of age are acute. Fibrosis is unknown and calcification is rare. Healing does not occur, and no encapsulated lesions are encountered. Even when only a single tuberculous focus exists in the body of an infant, it is the experience at the Babies' Hospital that the process in that single focus is not a healed one.

Points of Entrance. Tubercle bacilli may enter the infant's body before or at the time of birth through the umbilical vein. After birth the chief portals of entry are the respiratory system and the digestive tract. Occasionally the skin may act as the entrance point for the tubercle bacillus, and the conjunctiva must be considered as a possible portal for a generalized tuberculous infection, since rare cases of primary tuberculous conjunctivitis in small children have been recorded.¹ Primary tuberculous infection by way of the genito-urinary tract is practically unknown in infancy.

I. Tuberculosis Acquired Before or During Birth Through the Umbilical Vein. Tubercle bacilli may be carried to the fetus through the umbilical vein, if the mother suffers from tuberculous endometritis and placentitis, or if she has a bacillemia at the time of the onset of labor without tubercles in the placenta. Tuberculous endometritis and placentitis are rare, though authentic cases are on record (Schmorl and Kockel,² Warthin and Cowie³). Should tubercle

bacilli be present in the mother's blood at the time of labor, they may enter the torn fetal placental vessels. In either case the bacilli are carried directly to the liver, and then through the inferior vena cava to the right heart and so on to the lungs, before reaching the spleen and other viscera. Consequently infants who die of congenital tuberculosis always show tubercles in the liver and in the lymph nodes draining that organ, and such tubercles are usually more numerous and represent an older stage of the tuberculous process than do those in any other viscus. The lungs in congenital infection are the seat of miliary tubercles without the presence of any single older focus. Congenital tuberculosis is not common, and only two cases have come under the writers' notice.

II. Tuberculosis Acquired after Birth Through the Respiratory Tract. Pirquet estimates that 95 per cent of the tuberculosis of infants is of respiratory origin. Calmette,⁴ on the other hand, believes that comparatively few cases originate in that way. In our experience 82 per cent of children under three years of age gave evidence that their tuberculosis had been acquired by inhalation.

Inspired tubercle bacilli are taken up by phagocytes at any point of the respiratory mucosa and carried into the lymph vessels which surround all branches of the bronchial tree, including the alveolar ducts. There are no lymph vessels around the air spaces beyond the alveolar ducts,⁵ but the intercellular spaces sooner or later communicate with lymphatics. The bacillus-laden phagocytes may be arrested at any point along the bronchial tree or in the alveolar wall. Again, they may encounter no obstruction until they reach the lymph glands at the hilum, where all lymphatics from the lung and pleura converge. From there the flow is upward to the thoracic duct, into the blood, to the right heart and immediately back to the lungs through the pulmonary artery. Consequently the lungs are doubly exposed; for such inhaled tubercle bacilli as are not arrested in the lungs, nor filtered out on their way through bronchial lymph glands, come back through the pulmonary artery and its capillaries before they reach the systemic circulation and the abdominal viscera.

The Primary Lesion. Wherever inhaled tubercle bacilli first multiply and elaborate their metabolic products, whether in the lungs or in the bronchial nodes, a specific inflammatory reaction results in the formation of tubercles, which then constitute the primary lesion. At autopsy the primary pulmonary lesion in an infant is usually a small cheesy nodule 0.25 to 1 cm. in diameter, surrounded by a zone of miliary tubercles. It may not be apparent on inspection of the lungs at autopsy because of its central situation, but it is palpable as a hard nodule. The lung substance in the immediate neighborhood may be pink in color and well aërated, or there may be a narrow zone of congestion or of consolidation. As a rule, however, the entire lesion is too small to be discovered on

physical examination of the lungs during life. Rarely, two nodules of about the same size may be present in different lobes.

When a lymph gland contains the primary focus, the gland may or may not be enlarged, and the tuberculous lesion may occupy all or only a part of the gland substance. The recent experimental work of Krause⁶ has shown that in guinea-pigs gross lesions in the lungs are not indispensable to the appearance of gross lesions in the tracheobronchial nodes. With this our autopsies on young infants agree.

The primary lesion may for a time remain the only one in the body. Since in children under two years of age the tendency is not toward encapsulation and healing, a focus rarely remains single for many months. In a slowly developing tuberculous lesion caused by a non-invasive strain of the tubercle bacillus, which remains latent for a time in one or two foci, small calcareous deposits may appear. It has happened three times that a single tuberculous focus in a bronchial lymph node has been encountered at autopsy, in children seventeen and eighteen months of age. The cause of death was pneumonia in one case, neoplasm of the kidney in another and esophageal stenosis following the ingestion of a solution of lye in the third. In these three instances the tuberculous lesion, though limited in extent and apparently quiescent, was cheesy in character and not encapsulated. The same was true in the case of an infant nine months old who died of bronchopneumonia and showed, at autopsy, a cheesy nodule with a small calcareous center in the upper lobe of the left lung and a cheesy tuberculous area in one bronchial node on the left side.

The primary lesion is found more often on the right side than on the left, and in the upper or middle lobe more often than in the lower.

Type A. Generalized Miliary Tuberculosis Without a Focus Demonstrable by Physical Signs. Tubercle bacilli in an active lesion in the lungs or bronchial lymph nodes must, of necessity, reach the blood stream rapidly, through the thoracic duct. Since the venous blood is sent to the lungs, miliary tubercles form in the lung substance which may remain well aerated, pink in color, and normal in consistency. The spleen is attacked as soon as the bacilli enter the systemic circulation, and bacilli not filtered out by the spleen go on to the liver and other organs. Cases of this kind are common in young infants, who then die of a more or less generalized miliary tuberculosis, a bacillemia. The first successful culture of tubercle bacilli from human blood was obtained by Faber⁷ in a postmortem case at the Babies' Hospital.

When the primary focus in the lungs cannot be demonstrated by physical signs—percussion, auscultation, etc.—the case belongs to the clinical type designated as general miliary tuberculosis without a focus demonstrable by physical signs, which includes

only a small proportion of the cases of tuberculosis in infancy. The diagnosis is usually not made before death.

CASE REPORTS. Illustrative case histories have been chosen of patients who have died in the Babies' Hospital and upon whom autopsies have been made.

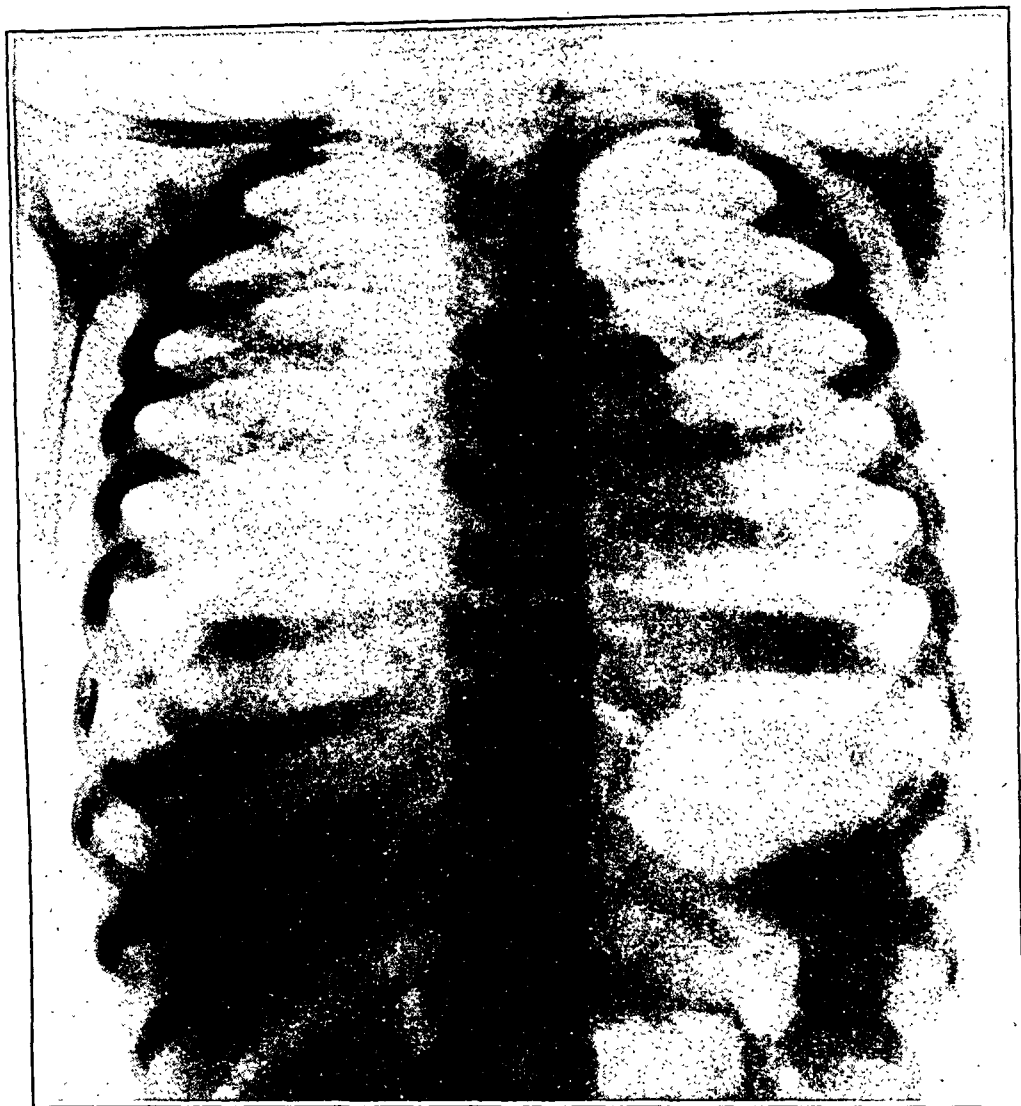


FIG. 1.—Type A. Roentgenogram of military tuberculosis of the lungs without any demonstrable focus. Note the profusely and evenly scattered tubercles in both lungs.

CASE I. L. R., aged seven months.

Chief Complaint. Cough, five weeks; diarrhea, two weeks.

Family History. Mother coughs, has night sweats and has lost weight rapidly since the baby was born; 3 other healthy children.

Birth History. Normal delivery; weight 7 pounds.

Feeding History. Still being nursed; has never been weighed since birth, but was a plump baby.

Present Illness. Began five weeks ago with a "cold" which persisted; cough and some fever, with rapid loss of weight. For the past two weeks has been having four or five loose green stools each day. Appetite poor.

Physical examination showed a moderately rachitic, poorly nourished child with enlarged spleen and liver, many fine rales throughout both lungs, negative findings in the urine, no adenopathy, a positive tuberculin skin reaction and no tubercle bacilli in the sputum.

Diagnosis. Rachitis; miliary tuberculosis of the lungs.

Subsequent Course. During the six days preceding his death, the child showed steady loss of weight with slightly irregular fever. He became drowsy and developed general rigidity. The spinal fluid was normal; it contained 15 cells but no tubercle bacilli. The blood count showed 9,000 leukocytes with 45 per cent polymorphonuclears.

At *autopsy* the anatomical diagnosis was acute miliary tuberculosis of the tracheobronchial lymph nodes, lungs, liver, spleen, kidneys; caseous tuberculous foci in lungs and tracheobronchial lymph nodes.

CASE II. C. E., aged five months.

Chief Complaint. Vomiting; loss of weight for two months.

Family History. Mother has tuberculosis; 1 other healthy child.

Birth History. Normal delivery; weight 8 pounds.

Feeding History. Never nursed; formula not known.

Present Illness. Baby has been at preventorium for past month; sent there as "sick," without details.

Physical examination showed an emaciated infant with a positive tuberculin skin test, but without abnormal signs in the lungs and no tubercle bacilli in the sputum; no adenopathy.

Diagnosis. Marasmus.

Subsequent Course. During the five weeks that he was in the hospital the gain in weight was small. The temperature was subnormal most of the time. No abnormal physical signs developed in the chest.

At *autopsy* the anatomical diagnosis was: Acute miliary tuberculosis of lungs, liver, spleen and heart; caseous tuberculous foci in lungs and tracheobronchial lymph nodes.

DISCUSSION. CHIEF COMPLAINT. The chief complaint in Case II defines it as a disturbance of digestion; in Case I as a combination of disease of the digestive and of the respiratory tract. The chief complaint frequently gives no clue to the fundamental disturbance. A combination of persistent cough and loss of weight with some fever, should make one suspicious of miliary tuberculosis.

FAMILY HISTORY. If an infant has been exposed to individuals with active tuberculosis, one is justified in being apprehensive

that he has picked up the infection. In both illustrative cases there is a clear history of exposure.

FEEDING HISTORY. In the early period of infection the child may take his food well. As a rule, as the disease progresses, the nutrition retrogresses.

PREVIOUS ILLNESS. Case II had had no acute illness previous to admission. Case I had had a cold which persisted, and also loose stools. The absence of a history of previous illness in these patients is common.

GENERAL APPEARANCE. The notes on both infants mentioned their undernutrition. Case II did not appear acutely ill; Case I did. This confusing evidence is purposely emphasized to show how difficult it is to recognize a miliary tuberculosis from the general appearance of the infant. The presence of cyanosis without adequate reason is helpful, directing the attention to tuberculosis.

CHEST. The physical examination of Case II showed nothing abnormal in the lungs. An examination of Case I showed general bronchitis. It is impossible to elicit abnormal physical signs from a lung containing only miliary tubercles. The presence of an associated bronchitis which persists with proper treatment, may suggest a general miliary tuberculosis. The roentgen-ray furnishes the only help to a demonstration of miliary tubercles in the lungs. Multiple small abscesses in the lungs may, though rarely, give a similar roentgenogram, and lead to confusion in the interpretation of the plate. Multiple peribronchial pneumonic areas also give a roentgen-ray picture like miliary tuberculosis; they are frequent in cases of influenzal pneumonia.

ABDOMEN. The liver is usually enlarged in general miliary tuberculosis. However, the edge of the liver is felt in so many infants that little help is offered by this sign. The enlargement of the spleen is frequent. This physical sign is emphasized.

LYMPH NODES. In both infants there were no abnormal enlargements. In infants under a year of age tuberculosis of the cervical lymph nodes is not common.

THE COURSE OF THE DISEASE OBSERVED BY THE PHYSICIAN.
FEVER. The temperature of Case II was subnormal through her five weeks stay in the hospital; Case I's temperature fluctuated between 99° and 102° F., one day reaching 103° F. This fluctuating temperature is more common than the subnormal type. Reference is made to the latter form to guard against dismissing general miliary tuberculosis because of a subnormal temperature.

RESPIRATION. There is no significant variation in the breathing.

VOMITING. Apparently there is no significant association between vomiting and a general miliary tuberculosis, unless there is a focal lesion in the brain.

BOWELS. The stools are as likely as not to be normal, and this is true even if there are ulcers in the intestines.

SPECIAL TESTS. The tuberculin skin test is a valuable aid in determining the presence or absence of general miliary tuberculosis of the type under consideration. A positive reaction in children under two years of age means a tuberculous infection and is significant. The test may be negative in tuberculous infants who are moribund or who are in a condition of extremely low resistance. It is urged that the test be made more than once if the first attempt is negative. The intradermal test is more sensitive than the Pirquet test.

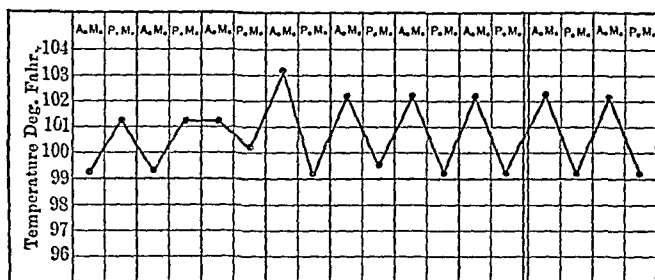


CHART I.—Case I, "L. R."

LABORATORY EXAMINATION. *Sputum:* In the great majority of infants who have a general miliary tuberculosis without demonstrable focus, tubercle bacilli are not found in the sputum. *Blood Count:* The white cells may be normal in number or they may be increased to 20,000 or 30,000. It is, however, unusual to see the white cells above normal in a general miliary tuberculosis, unless there is a secondary bronchopneumonia or bronchitis. It may be stated that the blood count is of little value.

PROGNOSIS. Fatal in every case.

COMMENT. Attention is called to the finding of caseation of the lungs at autopsy in both cases. These caseous foci were too small to be demonstrated by the usual method of physical examination.

Type B. Generalized Miliary Tuberculosis with a Focus Demonstrable by Physical Signs—Bronchopneumonia, Simple and Cheesy. A child who has a miliary tuberculosis sometimes acquires a non-tuberculous bronchopneumonia which may cause his death. At autopsy the lungs are swollen, heavy, red, and show an extensive consolidation of bronchopneumonia in the greater part of one or more lobes, with gray or yellow tubercles in large numbers scattered over both lungs.

On the other hand, cheesy bronchopneumonia may develop: the primary pulmonary focus spreads locally, a wider zone of tubercles forms around it and the alveoli of the surrounding lobules become filled with exudate which rapidly undergoes coagulation necrosis. Small areas of cheesy bronchopneumonia result and by

their coalescence more or less of one lobe may become involved. Often the earliest cheesy areas develop about small bronchi and give a characteristic clover-leaf effect to the lesion. The lung substance between the cheesy areas may remain pink and aerated for a time, but soon becomes dark red and solid. If softening of a cheesy area occurs a cavity results. The cavity usually opens into a bronchus. It may be only 0.5 cm. in diameter or it may involve the greater part of a lobe. Pulmonary hemorrhage is very rare in young children, although bloodvessels of appreciable size may be seen in the walls of a cavity.

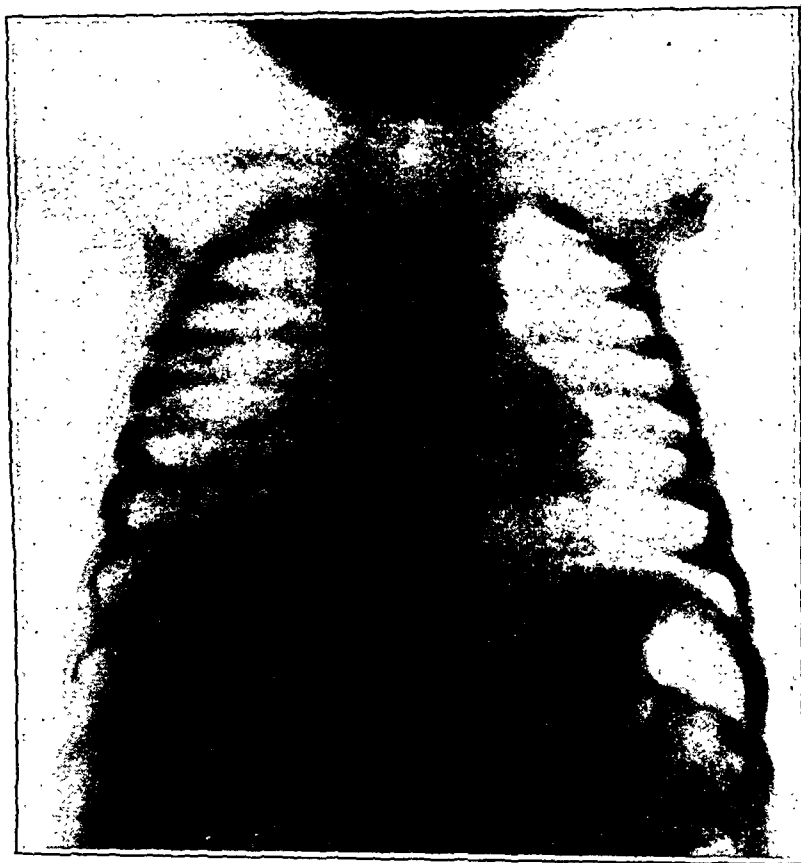


FIG. 2.—Type B. Roentgenogram of tuberculous pneumonia in right lower lobe with small cavity in center, cheesy pneumonia with smaller cavity in left lower lobe, and miliary tubercles over both lobes.

In cheesy bronchopneumonia many tubercle bacilli are present in the sputum. The swallowing of tubercle-bacillus-laden sputum may lead to the formation of ulcers in the small and large intestines. The ulcers may be present in the duodenum, and may extend to the rectum.

The bronchial lymph nodes at this stages have usually become enlarged to one or more times their original size, with extensive areas of cheesy degeneration and softening due to suppuration. Many tubercle bacilli are present in such softened nodes.

CASE III. R. G., aged six months.

Chief Complaint. Cough, two months; fever, one day.

Family History. No tuberculosis.

Birth History. Normal delivery; weight 8 pounds.

Feeding History. Nursed for fifteen days, then milk formula; did well.

Previous Illness. Baby had been at hospital with bronchopneumonia three weeks ago, and had only done fairly well since.

Present Illness. Baby has had a slight cold for over two months; no vomiting; seems hungry; fever began this morning, amount not known; stools two or three a day, fair; baby gaining very slowly.

Physical examination showed a poorly nourished, fretful, rachitic infant, with slight dyspnea, diminished resonance over the base of the right lung and in the right axilla, and many moist rales, more numerous over the right lung behind; no tubercle bacilli found in the sputum.

Provisional Diagnosis: Bronchopneumonia.

During the next three weeks, the pulmonary signs persisted, the weight decreased, and death occurred after two days of marked prostration and cyanosis.

The *anatomical diagnosis* was: Rickets; acute miliary tuberculosis of lungs, liver, spleen, kidneys, mesenteric lymph nodes; caseation of tracheobronchial lymph nodes and lungs; fibrinous pleurisy; acute catarrhal bronchitis.

CASE IV. M. K., aged thirteen months.

Chief Complaint. Cough; loss of weight for five months.

Family History. Mother has tuberculosis.

Birth History. Normal delivery; weight 9 pounds.

Feeding History. Nursed for three months; milk from Board of Health Station for two months; condensed milk for eight months. For last six weeks has also had oatmeal, zwieback, etc.

Previous Illness. Seemed perfectly well until five weeks ago.

Present Illness. Began slowly with cough and stationary weight; during the last few weeks has been losing weight, when three months old, weighed 13 pounds; has slight fever occasionally; coughs mostly at night and generally very loose; three weeks ago spat up a little blood.

Bowels. Regular; stools good.

Physical examination showed an emaciated white male child who appeared chronically ill, weak and prostrated, with rapid respirations and some dyspnea, but no cyanosis. Tuberculin skin test was positive and tubercle bacilli were found in the sputum.

During the three weeks in the hospital he lost weight, the pulmonary signs remained unchanged and an eruption of tuberculides resembling chicken-pox, developed. He became progressively weaker until he died.

Anatomical Diagnosis. Tuberculids of the skin; acute miliary tuberculosis of lungs, liver, spleen, peritoneum, kidneys; caseation of lungs, tracheobronchial, mesenteric, cervical lymph nodes; cavitation of lung; tuberculous pleurisy; tuberculous enteritis; fatty and congested liver.

DISCUSSION. CHIEF COMPLAINT. A review of a number of case histories of this type of tuberculosis shows that cough, fever, and loss of weight, rapid respiration and occasional vomiting appear in the chief complaint in different combinations.

FAMILY HISTORY. It is probable that in a large majority of tuberculous infants a history of exposure to tuberculosis could be traced if a searching investigation were carried out.

PREVIOUS ILLNESS. It is rather striking that no history of previous illness can be obtained in a considerable proportion of infants with tuberculous bronchopneumonia. There is no doubt that a predisposition to tuberculosis is determined by an attack of measles or whooping-cough. Persistent cough, fever, and loss of weight following these diseases may reasonably make one suspicious of tuberculous infection.

PRESENT ILLNESS. This is summarized in the chief complaint. Case IV gives a history of spitting blood, which is not usual in infants. This point is especially emphasized.

CHEST. It is impossible, unless there are signs of a cavity, to differentiate tuberculous bronchopneumonia from a non-tuberculous bronchopneumonia by physical signs. The determination of the tuberculous character of the lesion must be made by an examination of the sputum, by a skin test, by a history of exposure, and by the duration of the disease. A tuberculous bronchopneumonia is likely to have a longer duration than a non-tuberculous bronchopneumonia. It must not be forgotten that a simple bronchopneumonia is often superimposed on a pulmonary tuberculosis and adds confusion to the diagnosis.

LYMPH NODES. It is not common to find the superficial lymph nodes involved in tuberculous bronchopneumonia, but roentgen-ray examination of the chest will show an enlargement of the mediastinal nodes in the majority of cases.

SKIN. Tuberculids of the skin often look like the eruption of chicken-pox and are easily mistaken for it. Tuberculids in infants establish the diagnosis of a general tuberculosis of which tuberculous bronchopneumonia may be a focal manifestation.

THE COURSE OF THE DISEASE OBSERVED BY THE PHYSICIAN. FEVER. Case III's temperature chart may be studied as representing a composite of the different types of temperature found in tuberculous bronchopneumonia. Probably the most usual type is that represented in the first week—a remittent fever. A second type is represented in the complete chart—a combination of remittent temperature, and normal and subnormal temperatures; and a third

type is that represented by the subnormal phase of the temperature. Tuberculous bronchopneumonia in infants may run its course with a subnormal temperature, though this is not usual.

RESPIRATION. The breathing in tuberculous bronchopneumonia is frequently more rapid than would be accounted for by the physical signs.

NUTRITION. In an infant, carefully fed, a steady loss of weight in association with physical signs of bronchopneumonia is one of the most important evidences of the tuberculous nature of the disease.

SPECIAL TESTS. If an infant has a demonstrable focus in the lungs the likelihood of finding tubercle bacilli in the sputum is much greater than in Type A, where there is no demonstrable focus. It is essential that repeated examinations be made.

BLOOD COUNT. The total leukocyte count is more often over than below 10,000 and the polymorphonuclears are more often over than below 50 per cent of the white cells. This high leukocyte count may be accounted for in many cases by a complicating bronchopneumonia.

COMMENT. Cavitation is frequently present in tuberculous bronchopneumonia, even in young infants, especially if there is an extensive involvement of the lungs. The detection of a cavity is an important contribution to the diagnosis.

There may be a tuberculous ulceration of the intestines without symptoms or physical signs referable to the intestinal tract. It was so with Case IV.

PROGNOSIS. Probably every infant dies who has a tuberculous bronchopneumonia as a part of a general miliary tuberculosis. There has been no case of tuberculous bronchopneumonia at the Babies' Hospital without a dissemination of tubercle bacilli in other organs. The younger the infant, the less likelihood there is for a tuberculous process to confine itself to the lungs.

Type C. General Miliary Tuberculosis with Focal Lesions in the Meninges—Tuberculous Meningitis. Tuberculous meningitis terminates about 40 per cent of all cases of general miliary tuberculosis in children under two years of age. It occurs in a much higher percentage of cases which originate by inhalation of the tubercle bacilli than by ingestion. At the Babies' Hospital the bovine type of tubercle bacillus was found in 3 cases of tuberculous meningitis following a primary lesion in the digestive tract. In the great majority of cases, however, it is the human type of bacillus which is found in the spinal fluid.

At autopsy miliary tubercles are present in smaller or larger numbers along the vessels of the pia mater over all the surfaces of the brain and cord. Often they are also found in the choroid plexus and over the floor of the lateral ventricles. An exudate of serum and fibrin is usually limited to the base of the brain, where it infiltrates the pia in the interpeduncular space and over the isles

of Riel. It may spread to both surfaces of the cerebellum. Rarely such an exudate extends along the vessels over the surface of the cerebral hemispheres. The ventricles as well as the Sylvian aqueduct may be more or less dilated, following closure of the foramina of Luschka and Magendie by inflammatory exudate.

Tuberculous masses 0.5 to 2 cm. in diameter are encountered in the substance of the cerebrum or of the cerebellum in about 2 per cent of cases of tuberculous meningitis in young children. These lesions have a cheesy center which may undergo softening. The pia mater over and near them is usually studded with tubercles.

In rare cases tuberculous meningitis may be complicated by the presence of the meningococcus, the Pfeiffer bacillus, the pneumococcus or the streptococcus. All these bacteria cause a purulent inflammation of the meninges which obscures both the clinical and the pathological picture, making a correct diagnosis difficult during life. No case of recovery from tuberculous meningitis has ever been observed at the Babies' Hospital.

CASE V. D. B., aged eight months.

Chief Complaint. Drowsiness, one week; stupor, three days; slight cough, one month.

Family History. Tenth child; father tuberculous.

Birth History. Normal delivery; small baby.

Feeding History. Nursed for three months, then fed condensed milk; gained well.

Previous Illness. None.

Present Illness. Has had a slight cough for a month; for the past week has been drowsy, but could be roused; for three days baby has been in stupor; no convulsions; very constipated; appetite poor.

Examination showed a well nourished infant, drowsy, with bulging fontanelle, slow respirations, palpable liver and spleen, marked tache, hyperactive knee jerks and double Babinski.

The child became comatose and died the day after admission.

Anatomical Diagnosis: Acute miliary tuberculosis of brain, meninges, vocal cords, lungs, liver, spleen, kidneys; tuberculous caseation of tracheobronchial lymph nodes.

CASE VI. J. C., aged nineteen months.

Chief Complaint. Constipation, three weeks; drowsiness, three days; convulsions, twelve hours.

Family History. No tuberculosis; 1 other child well; 1 died of pneumonia four months ago.

Birth History. One of twins; normal delivery; weight $5\frac{1}{2}$ pounds.

Feeding History. Bottle-fed since birth; at present getting whole milk and farina.

Present Illness. Except for constipation was well until two weeks ago when he became irritable; no vomiting; had slight fever; refused

food; three days ago became drowsy; has been getting worse and is never awake at present; had general convulsion twelve hours ago, lasting fifteen minutes; face has twitched since convulsion; no cough.

Physical examination shows a poorly nourished negro male child, acutely ill, with spasticity of the whole right side, tonic spasms of the arm, leg, right face and neck, a fine nystagmus and an irregular strabismus, irregular respiration, few rales and diminished resonance over apices. Babinski, Kernig and tuberculin skin test positive.

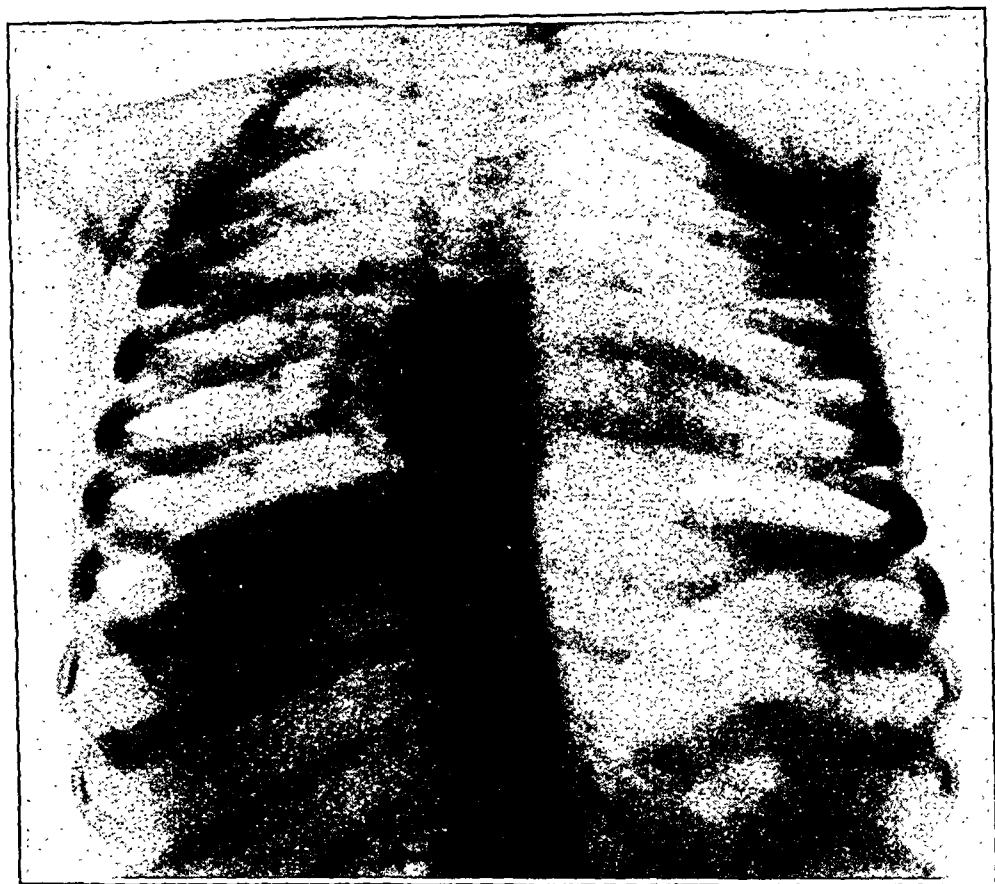


FIG. 3.—Type C. Roentgenogram of miliary tuberculosis in both lungs; cheesy area in right upper lobe. Death from tuberculous meningitis.

Provisional Diagnosis: Tuberculous meningitis; pulmonary tuberculosis.

During five days in the hospital, he had frequent convulsions, refused food, and became progressively more drowsy.

Anatomical Diagnosis. Acute miliary tuberculosis of meninges, lungs, pleura, liver, spleen; tuberculous caseation of tracheo-bronchial and mesenteric nodes; tuberculous enteritis.

DISCUSSION. CHIEF COMPLAINT. Practically every patient with tuberculous meningitis is admitted to the hospital with a history of drowsiness or stupor as one of the symptoms in the chief complaint. The combination of symptoms which point most signifi-

cantly to tuberculous meningitis is drowsiness, irritability and vomiting. The reason for the comparative infrequency of convulsions in the early stages of the disease is easily explained by the fact that the lesion is located with greatest intensity at the base of the brain. It is impossible to differentiate the drowsiness of tuberculous meningitis from that of encephalitis lethargica. If, however, there are associated with it symptoms of irritability it is more likely to be tuberculous meningitis.

DURATION. The duration of the disease from onset to death, at this period of life, is at the longest, three to four weeks.

FAMILY HISTORY. In most cases of tuberculous meningitis there must have been an exposure to an individual who has an active tuberculosis, since meningitis due to the bovine tubercle bacillus is comparatively rare.

FEEDING HISTORY. There is a curious idea that tuberculous meningitis is more commonly seen in poorly nourished children. It is seen as often in the well nourished. Many of the infants are breast fed. Constipation and occasional vomiting are almost constant symptoms. They may precede the onset of symptoms definitely referable to the central nervous system by a few days or weeks, but more often they appear at the time of the definite onset of the meningitis. The nutrition fails rapidly during the course of the disease. Vomiting, as a rule, is at infrequent intervals and may be absent. If the course of the disease is prolonged to two, three or four weeks the emaciation becomes extreme.

PREVIOUS ILLNESS. The fact which should be emphasized is that an infant may have been perfectly well up to the onset of a tuberculous meningitis.

GENERAL APPEARANCE. Drowsiness is perhaps the most common condition early in the disease. Signs of cerebral irritation appear as a rule in the first week. The infant may have one or more general convulsions; localized spasms are common; one side of the face, one arm, or one leg may twitch; the eyes are in bizarre forms of strabismus; nystagmus comes and goes; occasionally there may be periods in which the head and lower extremities are bent back; opisthotonos is often followed by relaxation. The variability in the location and duration of muscular spasms is almost characteristic of tuberculous meningitis. Constant rigidity of the neck is more characteristic of cerebrospinal meningitis than of tuberculous meningitis.

CHEST. There may be no physical signs, or there may be signs of a tuberculous bronchopneumonia.

EXTREMITIES. The infant will often hold the legs so stiffly that it is difficult to flex them. At other times they will be flaccid. A variability of stiffness and relaxation of the lower extremities is common.

REFLEXES. The knee-jerks are at times increased, at times normal or at times absent. Kernig's sign is usually present at some time in the course of the disease. The same variability is seen in the Babinski sign. A tache is present in practically every case.

COURSE OF THE DISEASE OBSERVED BY THE PHYSICIAN. The disease may run its course with a normal or a subnormal temperature. The more frequent type is a remittent fever. Irregularity in the rate and the depth of breathing is constantly observed. The heart action likewise shows irregularity in force and frequency.

SPINAL FLUID. The presence of a tuberculous meningitis is determined by examination of the spinal fluid for tubercle bacilli. They can be found in 95 per cent of all cases. This statement is made on the supposition of careful and prolonged search. The fluid is clear in most instance, but sometimes it is slightly turbid. If the fluid is allowed to stand in a test tube, a veil-like film forms. It gives the appearance of being suspended from the surface of the fluid. Since the fibrin entangles the bacilli, it is by spreading the film on a slide and staining it that the organisms are found. As a rule, the fluid is under increased pressure. The number of cells is increased. (Ten to 15 cells per cm. may be regarded as representing the maximum normal count.) The lymphocytes usually represent over 80 per cent of the cells. Rarely, and toward the end of the disease, the polymorphonuclear cells are more numerous than the lymphocytes. The test for globulin is positive.

COMMENT. It would be possible to select enough autopsy reports to demonstrate that miliary tubercles were present in practically every organ of the body. Tuberculous meningitis in infancy is part of a general miliary tuberculosis, dissemination of the tubercle bacilli being by way of the blood stream. This will explain the high death rate in early life. Rarely, and in children over two years of age, the lungs, liver, and spleen may escape, and the cerebrospinal meninges may be attacked first by the tubercle bacilli which have entered the blood stream from a tuberculous focus in a bronchial lymph node. We have seen two cases of this kind in children over two years of age.

PROGNOSIS. Probably fatal in every case in infants under two years.

TREATMENT. None.

III. Tuberculosis Acquired After Birth Through the Digestive Tract. Tubercle bacilli may enter the mouth of a child with food, or they may be carried there by the child's fingers, toys, or utensils, or by the fingers of his attendants. The results of such ingestion vary with the course taken by the bacilli, and the point at which they are arrested.

(a.) The tonsils may arrest the bacilli, become the seat of tuberculous inflammation and discharge tubercle bacilli into the cervical lymph nodes which drain the tonsil; or the bacilli may reach these

nodes without the development of a tonsillar lesion. General tuberculosis from such a source is of slow development, and of rare occurrence in children under two years of age. We have not met such a case in an infant.

(b.) When tubercle bacilli are swallowed, they usually pass through the stomach with the food into the intestines, where they are carried by phagocytes into the lymphatics. They may leave the intestinal wall without starting any lesion there, but the mesenteric lymph nodes will filter some of them from the lymph stream and become the seat of tuberculous inflammation. The process is similar to that which takes place in the respiratory tract. If the tubercle bacilli are few and of low invasive power, one node may be able to filter them all, and then if no more bacilli are ingested, the lesion in the node may remain inactive for months and even become calcified. But in children under two years of age completely healed tuberculous lesions have not been encountered by us, and sooner or later bacilli in the lymph node are stimulated to multiply, and, entering the lymph stream, reach the general circulation, to localize in any organ prepared for them. The youngest child in whom we have encountered tuberculosis limited to one mesenteric node was two years and ten months old.

(c.) Tubercle bacilli may pass through the intestinal wall and form tubercles in several mesenteric glands and in the peritoneum, causing extensive tuberculous peritonitis and finally more or less generalized tuberculosis.

(d.) Finally, swallowed tubercle bacilli may localize in the lymph follicles of the intestinal wall at any level, and form typical ulcers. Large numbers of bacilli may enter the lymphatic vessels from these ulcers and cause typical lesions in the mesenteric nodes and the peritoneum. Eventually the bacilli reach the celiac plexus, the thoracic duct and the general circulation.

In cases of primary tuberculosis of the digestive tract, with or without peritonitis, the lungs and tracheobronchial lymph nodes may be entirely free from tuberculous lesions. But if the child lives long enough, miliary tuberculosis in the lungs and their lymph nodes results. The age of the lesions above and below the diaphragm is distinctly different, however.

The stomach is infrequently the seat of tuberculous lesions. Only in a very generalized tuberculosis are typical ulcers formed on the gastric mucosa. They are usually small, 1 to 3 mm. in diameter, one or two in number, along the greater curvature or in the posterior wall in the pyloric half of the stomach. They cause no clinical symptoms. The ulcers involve all the coats of the organ, as in the intestines.

Tuberculous Peritonitis. Tuberculous peritonitis is found less often in young infants than in children over two years of age. It is almost

invariably the result of primary tuberculous infection of the digestive tract, and the mesenteric lymph nodes are practically always the seat of tuberculosis, although the intestines may be quite free. In most cases, however, there are extensive tuberculous ulcers in the small intestine. The mesenteric nodes may be markedly enlarged, sometimes forming masses 4 to 6 cm. in diameter.

DIAGNOSIS. The usual history in these children is that: (1) The abdomen has gradually increased in size; (2) there is discomfort and pain in the abdomen; (3) there is slight intermittent fever; and (4) there is constipation. The enlargement of the abdomen must be distinguished from that seen in chronic intestinal indigestion. An important difference is that in the latter condition the size of the abdomen varies at different times of the day. It is usually large after meals and almost always larger at night than in the morning. In tuberculous peritonitis the circumference of the abdomen is not so likely to vary in size. To determine this point, it is necessary to measure the abdomen at different times of the day. If the abdomen is carefully palpated one finds masses in tuberculous peritonitis. Perhaps the most common location of these tumors is above the navel extending across the abdomen. This represents a rolled up omentum in a mass of tuberculous adhesions. Such masses are not found in chronic intestinal indigestion. If in this condition there are fecal accumulations which might be taken for tuberculous masses, a cathartic will get rid of them.

Tuberculous peritonitis (in very young children) associated with a large quantity of fluid in the abdomen is not so common as is the fibrinous form.

The tuberculin skin test should be made as an aid in interpreting the condition. After two years of age a positive reaction is not so significant as in early infancy. It cannot, however, be disregarded.

In the case of a very generalized tuberculosis following infection by inhalation, especially in young infants, the peritoneum may be invaded, as any other organ may be, and no special symptoms result.

TREATMENT. Surgical treatment has proved most unsatisfactory. A gradually increasing time exposure to the sun's rays with proper food, and plenty of fresh air, offer the best hope of improvement. It is important to begin with an exposure of ten to fifteen minutes and to increase by five to ten minutes each day up to several hours a day. The outlook is better if the skin of the abdomen tans. This treatment can be carried out at home.

IV. Tuberculosis Acquired After Birth Through the Skin. Any simple lesion or surgical wound of the skin may become the primary focus from which a generalized tuberculosis may develop. In young infants the wound of a circumcision operation has occasionally proved such a focus, feeding bacilli to the neighboring inguinal lymph nodes, causing typical lesions. The lesion in the wound and

lymph nodes constantly feeds bacilli to the lymph stream and consequently to the blood. Dr. Holt⁸ has recorded such a case.

General tuberculosis has been reported as resulting from the infection of a small skin lesion. So in Sheltema's⁹ case, a tuberculous father cared for his child who had a small sore on the forehead.

Type of Tubercle Bacillus Infection. The human type of tubercle bacillus is by far the most frequent cause of tuberculous infection in young children. Park and Krumwiede¹⁰ estimate that bovine infection causes less than 10 per cent of the total deaths from tuberculosis in young children. In this country, the proportion is lower than it is abroad, especially in Great Britain. An unselected series of fatal cases from the Babies' Hospital was studied by Park and Krumwiede, who found 6.33 per cent due to bovine type of tubercle bacillus. In England, Cobett¹¹ found that 33 per cent of all the children under five years who die from tuberculosis are infected with bovine bacilli. This type of tubercle bacillus causes the majority of infections of the cervical lymph nodes, of the alimentary tract and of the peritoneum, while the human type causes pulmonary tuberculosis and the great majority of cases of meningitis. Only about 4 per cent of tuberculous meningitis is due to the bovine bacillus. Mixed infection with human and bovine bacilli may take place, the pulmonary lesions in such cases being due to the human type and the abdominal lesions to the bovine type of bacilli. Finally, both types have been found in the bronchial nodes.

Significance of Positive Tuberculin Skin Tests. 1. *In infants under six months without symptoms or physical signs of tuberculosis:* The statement may be ventured that over 75 per cent of such infants will develop tuberculosis within the first year of life. This is tantamount to saying that the infant will die of tuberculosis within one year.

2. *In infants between six and twelve months without symptoms or physical signs of tuberculosis:* One is warranted in saying that 50 per cent or more will develop tuberculosis within a year; or in other words, they will die of it within that time.

3. *In infants between one and two years without symptoms or physical signs of tuberculosis:* Between 25 and 50 per cent will develop the disease. There is a better chance of their escaping a fatal outcome.

General Conclusions. The seriousness of tuberculosis in infancy is evident. If one realizes that a majority of the infants under a year of age with tuberculosis are killed by it, regardless of treatment, one may well ask, what is to be done? The only answer to this question is that every infant must be kept away from those who have tuberculosis. The only treatment for tuberculous infants is preventive; that means absolute isolation from anyone who has tuberculosis. This obviously is best accomplished by the isolation of the tuberculous individual.

REFERENCES.

1. Ginestous: *Ophthalmologie Infantile*, Paris, 1922, p. 191.
2. Schmorl and Kockel: *Ziegler's Beitr. z. path. Anat.*, 1894, 16, 313.
3. Warthin and Cowie: *Jour. Infect. Dis.*, 1904, 1, 140.
4. Calmette: *L'Infection Bacillaire et la Tuberculose*, Paris, 1922.
5. Miller: *Am. Rev. Tuberc.*, 1919, 3, 193.
6. Krause: *Am. Rev. Tuberc.*, 1920, 4, 135.
7. Faber: *Jour. Am. Med. Assn.*, 1914, 63, 1656.
8. Holt: *Arch. Ped.*, 1913, 30, 697.
9. Sheltema: *Kinderheilk.*, 1914, 80, 118.
10. Park and Krumwiede: *Studies from the Bureau of Laboratories*, New York Health Department, 1912-13, 7, 88.
11. Cobbett: *The Cause of Tuberculosis*, Cambridge, 1917.

COMPARISON OF THE BLOOD-PLATELET COUNT IN SPLENIC ARTERIAL AND VENOUS BLOOD.*

BY JACKSON K. HOLLOWAY, M.D.,

FELLOW IN SURGERY, MAYO FOUNDATION, ROCHESTER, MINN.

AND

LAUNCELOT M. BLACKFORD, M.D.,

VOLUNTARY ASSISTANT IN PATHOLOGY, MAYO FOUNDATION, ROCHESTER, MINN.

SINCE Kaznelson⁷ recommended splenectomy for cases of thrombocytopenic hemorrhagic purpura, surgical treatment has been followed in 16 cases with brilliant results (Giffin).² Many theories have been advanced in an attempt to explain why splenectomy has such a desirable effect, but a satisfactory explanation of the phenomenon is lacking. The outstanding findings in thrombocytopenic hemorrhagic purpura are prolonged bleeding-time, irretractability of the blood clot, and a marked reduction in the number of the blood platelets in the peripheral capillary circulation. Prolonged bleeding-time and non-retracted clot probably depend largely on the insufficient number of blood platelets present (100,000 or less) (Gram).⁵ It is, therefore, of prime importance to determine, if possible, the cause of the reduced number of blood platelets.

As platelet counts vary within wide limits, partly because of technic, even in persons suffering from acute exacerbations of purpura, and as splenectomy is followed by a marked and almost immediate rise in the platelets, it is reasonable to assume that there is no lack of production in this disease, but rather an increased destruction of this important blood corpuscle. It is most commonly believed that hemorrhagic purpura is the result of an infectious

* Work done in the Department of Experimental Surgery and Pathology and Section on Medicine, under the direction of Dr. H. Z. Giffin.

process, with the production of some toxic material which rapidly destroys blood platelets. The toxin affecting these changes is perhaps a secondary substance, the production of which is initiated by the pathological process, possibly some abortive substance originally designed to protect (Giffin and Holloway).³ It is possible that this process is closely linked with protein intoxication and anaphylaxis (Glanzmann).⁴ As splenectomy has been followed by such a remarkable rise in blood platelets, together with a disappearance of clinical symptoms, it is to be assumed that the pathological process which leads to the excessive destruction of platelets has its basis in the lymph glands and hemolymph glands, Kupffer cells of the liver, and probably in other parts of the reticulo-endothelial apparatus, of which the spleen is a major member.

In 2 cases in which operation was performed for hemorrhagic purpura, it is reported that the blood from the splenic vein contained fewer platelets than blood from the peripheral circulation. In the case operated on by Cori,¹ the counts were 1200 in the splenic vein and 4000 in the peripheral vein. In the case in which operation was performed at the Mayo Clinic, the splenic vein showed a count to 40,000 as compared with 80,000 in the capillary circulation (Giffin).² These counts, however, are so low that they cannot alone be a basis for conclusions. It is, however, impossible to judge how satisfactorily these observations were carried out. With these findings in mind, we have undertaken to ascertain: (1) Whether the platelet count of blood from the splenic vein differed from that of the splenic artery; and (2) whether there was any difference in counts made of the blood from the peripheral veins and peripheral arteries in normal dogs.

The comparison of red blood cells in the splenic vein and the splenic artery has been made by Krumbhaar and Musser,⁸ and others. Their figures for red and white blood cells, differential counts, and total hemoglobin show that the blood of the splenic vein does not differ greatly from that of the artery, and that all variations were "within the limit of error inherent in the methods of blood examination."

Method of Experimentation. Active and well nourished dogs were selected, but 1 of them (Experiment 2) had distemper at the time the counts were made. Ether was used as an anesthetic. The spleen was gently drawn through the abdominal wound and wrapped in pads moistened with warm sodium chloride solution. Great care was exercised to disturb the organ or vessels as little as possible, bearing in mind that congestion of the spleen causes greatly increased content of blood from the splenic vein.^{6, 9} With an aneurysm needle the splenic vein and artery were carefully isolated and dissected, the fields being kept very dry. Blood from the vein was taken first. With a small Graefe knife a venipuncture was made, which afforded an abundant supply of blood coming from

the spleen. Several samples were thus secured in Thoma counting pipettes, fresh sodium citrate solution being used as a diluent. The vein was then clamped across the bleeding point without obstruction to the circulation. Similar methods afforded samples from the arterial circulation. That we might control our experiments as well as possible, we secured at the same time samples of blood from the splenic vein and artery for counting red blood cells and white blood cells. In Experiments 5 to 10, inclusive, a diluting solution consisting of 3.8 per cent sodium citrate and 0.2 per cent formaldehyde (modification of method devised by Rees and Ecker)¹⁰ was employed, because of the claim that the presence of formaldehyde prevents the disintegration of cells and the formation of the so-called Arnold bodies. In the other experiments a 2 per cent solution of sodium citrate was used, and this has been adopted routinely. All counts were made on Levy chambers. Each sample of blood was counted by two or three persons, thus securing from four to six counts on the samples taken. Similar methods were employed in securing counts from the jugular vein, carotid artery and femoral vessels. By comparing our findings in specimens of blood taken from areas supplying various types of tissues, we were enabled to control our results even more closely than would be possible by comparing the erythrocyte and leukocyte counts in the splenic circulation. Furthermore, the work was done by a trained unit. We feel assured, therefore, that our range of technical error was reduced to a minimum. Even with such care, there appeared at times rather marked variations in the individual platelet counts. It is possible that these were due to variations in platelet content of the various blood samples, which were taken over periods of several minutes. However, we quite agree with other observers that the counting of blood platelets is somewhat unsatisfactory, and that rather generous limits should be allowed for error. Indeed, variations in counts ranging as high as 100,000 are not uncommon. The relationship between the counts of arterial as compared with venous blood was usually constant. (Table I). Tables I and II show the results of our experiments on 20 dogs. Eight of these dogs were used as controls in estimating the counts on blood from the peripheral vessel; the external jugular vein and the common carotid artery were used in 4, and the femoral artery and vein were used in 4.

Discussion. With the exception of 3 instances (Experiments 2, 4 and 11) venous blood was found to have a slight to fairly marked increased platelet count as compared with the arterial; this applies not only to the splenic vessels, but to the peripheral vessels as well. We offer no explanation for this difference. Krumbhaar and Musser point out that venous blood often shows more or less marked anisocytosis, and an inequality of staining which are not seen in blood from the artery, and that control smears from peripheral veins

TABLE I.—PLATELET, ERYTHROCYTE, AND LEUKOCYTE COUNTS OF FROM THE SPLENIC ARTERY AND VEIN OF DOGS.

Experi- ment.	Blood platelets.						Erythrocytes, millions.		Leukocytes.		
	Splenic artery.			Splenic vein.			Per cent venous compared with arterial. Arterial equals 100 per cent.	Splenic artery.	Splenic vein.	Splenic artery.	Splenic vein.
	Highest count.	Lowest count.	Average, 4 to 8 counts.	Highest count.	Lowest count.	Average, 4 to 8 counts.					
1	384,000	358,000	371,000	450,000	424,000	437,000	117.9	5.32	5.26	11,350	10,750
2	316,000	184,000	266,000	158,000	98,000	122,000	45.9	5.21	6.03	31,750	31,250
3	960,000	196,000	164,000	430,000	324,000	344,000	209.8	4.52	4.55	32,600	28,500
4	512,000	236,000	331,000	598,000	318,000	324,000	94.8				
5	152,000	124,000	137,000	284,000	190,000	244,000	178.1	4.85	4.78	20,900	22,200
6	74,000	19,000	49,000	148,000	51,000	104,000	212.2	4.82	4.53	14,400	17,500
7	122,000	32,000	74,000	120,000	52,000	88,000	118.1	5.11	4.97	13,900	16,400
8	262,000	62,000	124,000	330,000	121,000	187,000	150.8	5.10	4.97	12,900	13,500
9	216,000	84,000	138,000	220,000	164,000	182,000	132.0	2.97	2.93	31,400	32,100
10	174,000	146,000	158,000	236,000	216,000	225,000	143.0	5.89	5.90	18,400	18,700
11	564,000	406,000	453,000	342,000	302,000	300,000	66.0				
12	295,000	269,000	282,000	476,000	452,000	464,000	164.5				

show changes in the red cells similar to those in the red cells from the splenic vein, which indicates that these changes are characteristic of venous blood in general. However, only materially improved methods of studying blood and counting platelets can determine accurately what is the normal difference between venous and arterial counts. We have proved to our satisfaction that in the dog the platelet content of the splenic vein is not normally reduced below that of the splenic artery. This fact is in keeping with physiological principles, for there is no reason for assuming *a priori* that the platelets or any other blood corpuscle should be materially reduced in number, under normal conditions, by a single passage through the spleen.

TABLE II.—PLATELET COUNTS IN PERIPHERAL VESSELS OF DOGS.

Experiment number.	Blood platelets.		Per cent venous compared with arterial. Arterial equals 100 per cent.
	Common carotid artery (average count).	External jugular vein (average count).	
13	355,000	462,000	130.1
14	210,000	360,000	171.4
15	148,000	197,000	133.1
16	97,000	261,000	270.1
	Femoral artery	Femoral vein	
17	316,000	365,000	101.1
18	76,000	342,000	450.0
19	115,000	197,000	171.3
20	122,000	314,000	257.3

The relationship of the spleen to platelet destruction in thrombocytopenic purpura has not yet been determined. The production in animals, by the injection of a specific antiplatelet serum, of a condition which most closely resembles hemorrhagic purpura is said not to be influenced by previous splenectomy (Sacerdotti).¹¹ In view of the fact that it has been demonstrated that normal venous blood in general shows higher platelet counts than arterial, the finding of reduced platelet counts in blood from the splenic vein as compared with the splenic artery in thrombocytopenic purpura would have especially definite importance. There would then be good grounds for assuming that the spleen is primarily concerned in the production of this syndrome, and that splenectomy is essentially a rational procedure.

Conclusions. 1. In a series of controlled experiments performed on dogs for the purpose of determining the relative platelet content of the splenic artery and vein, we have found that the blood-platelet content of the splenic vein is not normally below that of the splenic artery.

2. The blood-platelet content of the venous circulation in general is apparently slightly elevated over that of the arterial.

BIBLIOGRAPHY.

1. Cori, G.: Zur Klinik und Therapie (Splenektomie) der essentiellen Thrombopenie. *Ztschr. f. klin. Med.*, 1922, **94**, 356-369, Abstr., *Jour. Am. Med. Assn.*, 1922, **79**, 1186.
2. Giffin, H. Z.: Personal communication.
3. Giffin, H. Z., and Holloway, J. K.: Hemorrhagic Purpura, *Med. Clin. No. Am.*, 1923, **7**, 241.
4. Glanzmann, E.: Die Konzeption der anaphylaktoiden Purpura, *Jahrb. f. Kinderheilk.*, **91**, 391.
5. Gram, H. C.: On the Blood-platelets and the Bleeding-time in Diseases of the Blood, *Acta Med. Scand.*, 1920, **53**, 845.
6. Grigorescu, G.: (Quoted by Krumbhaar, E. B., and Musser, J. H., Jr.)
7. Kaznelson, P.: Verschwinden der hämorrhagischen Diathese bei einem Falle von "essentieller Thrombopenie" (Frank) nach Milzextirpation. *Splenogene thrombolytische Purpura*, *Wien. klin. Wchnschr.*, 1916, **29**, 1451.
8. Krumbhaar, E. B., and Musser, J. H., Jr.: The Relation of the Spleen to Blood Destruction and Regeneration and to Hemolytic Jaundice. X. Concerning the Supposed Regulatory Influence of the Spleen in the Formation and Destruction of Erythrocytes, *Jour. Exper. Med.*, 1914, **20**, 108.
9. Pribram, B. O.: Hypersplenische Hämophthisen und Stauungsmilz, *Wien. klin. Wchnschr.*, 1913, **26**, 1607.
10. Rees, H. M., and Ecker, E. E.: An Improved Method for Counting Blood Platelets, *Jour. Am. Med. Assn.*, 1923, **80**, 621.
11. Sacerdotti, G.: Sul siero antiplastrico. 2^a nota preliminare. *Soc. Cultori Science Med. e Nat.*, Cagliari, 6 April and 3 May, 1908; *Gior. d. r. Accad. med.-chir. di Torine*, 1908, **71**, 75. Abstr., *Biochem. Centrbl.*, 1909, **8**, 299.

TWO NEW ANTIMONY COMPOUNDS FOR INTRAVENOUS USE*

A STUDY OF THEIR THERAPEUTIC VALUE IN CASES OF GRANULOMA INGUINALE.

BY ALEXANDER RANDALL, M.D., F.A.C.S.

PHILADELPHIA.

(From the Urological Service of the Hospital of the University of Pennsylvania, Philadelphia, Pa.)

A PRELIMINARY report was published in 1923 on the use of two new synthetic antimony drugs, (sodium antimony thioglycollate and the triamid of antimony thioglycollic acid), in the treatment of granuloma inguinale. Included in this report was the result in therapy as observed in 3 cases. It is the purpose of this communication to complete the study of these drugs, present further evidence of their therapeutic value, to state their chemical composition and to incorporate toxicity studies in presenting them to the medical profession.

In the former article, 3 cases were cited of granuloma inguinale

* Presented in abstract before the Section on Medicine, College of Physicians, Philadelphia, October, 27, 1924.

in each of which splendid therapeutic results were obtained. In 1 of them a disease of fifteen years' duration was cured in seventeen days with but 9 intravenous injections, without reaction, and the patient proven free of recurrence six and a half months later. As such had not been accomplished before and only approached by treatment with tartar emetic; as this latter drug is known to be toxic; as its stability is questioned when subjected to heat for sterilization; as it presents at times alarming symptoms; as it has been held responsible for an occasional death; and as it (practically always when pushed to therapeutic effect, and even occasionally, when given in moderate doses) causes reactions in the way of bone aches, dyspnea, and so on, making some patients refuse its advantages; and finally as further experience has shown the therapeutic value and low toxicity of these new drugs to have far-reaching advantages over tartar emetic—it became desirable that our subsequent experience with them be published and that they be placed within the reach of all.¹

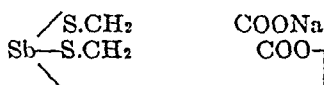
History. Sodium antimony thioglycollate (hereafter referred to as S. A. T. for brevity) has been known to chemists for a long time, while the triamide of antimony thioglycollic acid (hereafter referred to as T. A. T.) was first synthesized by Dr. John J. Abel, professor of pharmacology, Johns Hopkins University. Both drugs were the subject of two articles by Abel and Roundtree in experimental trypanosomiasis. Their experimental work on animals with these drugs, though carried on for trypanosome infections, gave sufficient scientific background as to their toxicity and efficacy to warrant the trial of their use in clinical cases without further animal studies, and even suggested their possible therapeutic value. This was fortunate as lesions of granuloma inguinale have not yet been successfully produced in the lower animals. One of them (T. A. T.) had never been used in man before. It was the preparation administered to the above cited case, of fifteen years' duration, in our preliminary report. Twelve or more years ago, Dr. Abel forwarded to some friends in India, some of the sodium antimony thioglycollate (S. A. T.) for use in kala azar and filariasis, but no report of its use has as yet been made, either to the profession or to Dr. Abel personally. So it might be said that the initial use of both drugs in infectious conditions in man occurred in the original cases of the preliminary report.

These original 3 patients were given the drugs as prepared and forwarded to me by Dr. Abel. Each consisted of 1 gm. in semi-crystalline form, and represented the last he had at the time in his possession. The striking therapeutic results seen in these 3 patients, stimulated the desire for further studies with the drugs,

¹ Samples of these drugs have been forwarded by Hynson, Westcott & Dunning, of Baltimore, to the Council on Pharmacy and Chemistry of the American Medical Association for their study.

and their synthesis was placed in the hands of Hynson, Westcott and Dunning of Baltimore. Through their coöperation and skill their preparation was furthered and the drugs purified into perfect crystalline substances in each case, and the following experimental work has been performed with material prepared by them.

Chemistry. 1. *Sodium antimony thioglycollate* (antimony sodium thioglycollate) is a white powder, very soluble in water and having a structural formula as follows:



Its antimony content is 37.17 per cent. The aqueous solution can be sterilized by boiling without chemical change other than the separation of a very small amount of antimony sulphide, which can be removed by filtration under sterile conditions.

2. *Triamide of antimony thioglycollic acid*, or possibly better called antimony thioglycollamide, crystallizes in white glistening plates, m. p. 116.5°–118° C. (uncorr.) and has the following structural formula:



Its antimony content is 30.77 per cent. At ordinary temperatures, 100 cc of water dissolves about 0.5 gm. When this solution is cooled, some of the compound crystallizes out. It is much more soluble in boiling water, from which it can be crystallized. When pure, it is stable in air, otherwise it turns yellow. A solution can be sterilized at boiling water temperature without chemical change, other than the separation of a trace of antimony sulphide, which can be removed by filtering under sterile conditions.

The presence of a precipitate of antimony sulphide is to be avoided in administering either drug. It appears as a rusty-colored sediment and probably increases the toxicity. It can always be safely removed by filtration.

Toxicity.* Toxicity studies with these two drugs have been carried on by intravenous and subcutaneous injections in mice.

The antimony content is as follows: T. A. T. 30.77 per cent; tartar emetic 36.16 per cent and S. A. T. 37.17 per cent, and in this ratio one might expect to find their toleration.

Tartar emetic was tried first to determine its point of lethal

* I am indebted to Dr. A. E. Bothe of the Urological Service for the study of the toxicity of these drugs. He carried out the work in the Laboratory of Surgical Pathology, University Hospital, under the guidance of Dr. A. N. Richards, professor of pharmacology, and with exceptional skill, accuracy and ingenuity, administered the intravenous injections in mice.

dosage on intravenous injection. Two out of 2 mice were killed inside of three hours' time by a dosage of 0.1 mg. per gram of body weight. Decreasing this to 0.08 mg. per gram of body weight, killed 3 out of 3 mice in the same length of time. When decreased to 0.05 mg. 2 out of 5 lived, and at a dosage of 0.025 mg. there were no deaths in 4 animals; thus fixing the safe dosage at the latter figure and the sure lethal dose at 0.08 mg. per gram of body weight.

The T. A. T. preparation showed a similar point of lethal dosage. It killed 3 out of 3 mice within three hours when given both in the 0.1 mg. and 0.08 mg. dosage. At 0.05 mg. per gram of body weight only 1 out of 4 mice died (75 per cent lived as compared to 40 per cent with tartar emetic in similar dosage) while with 0.025 mg. again 4 out of 4 lived. This shows slightly less toxicity, though the safe and lethal dosage remains the same.

The S. A. T. preparation was better tolerated. At the above lethal dosage of 0.08 mg. per gram of body weight, only 1 out of 4 mice died. Increasing the dosage to 0.1 mg., 5 out of 6 animals succumbed in from forty minutes to sixty hours, and only when 0.25 mg. was given was death caused in 2 out of 2 mice. Decreasing the dosage 0.05 mg., a slight discrepancy occurred and death in from twenty-four to forty-eight hours occurred in 2 out of 5 mice. (At this dosage, 75 per cent lived under T. A. T., 60 per cent lived under S. A. T., and only 40 per cent lived under tartar emetic.) Again at the dosage of 0.025 mg. per gram of body weight, 4 out of 4 lived. In this preparation, though the safe dose remains the same as tartar emetic and T. A. T., the higher doses appear to be less toxic. (Table I.)

TABLE I.—INTRAVENOUS INJECTIONS.

			Dose in mg. per gm. of body weight.					
			0.02	0.025	0.05	0.08	0.1	0.25
Tartar emetic	Injected	..	4	5	3	2		
	Died	..	0	3 ²	3 ¹	2 ¹		
T. A. T.	Injected	..	4	4	3	3		
	Died	..	0	1 ¹	3 ¹	3 ¹		
S. A. T.	Injected	1	4	5	4	6	2	
	Died	0	0	2 ³	1 ⁴	5 ⁵	2 ⁶	

¹ Deaths inside three hours.

² Deaths between six to forty-eight hours.

³ Deaths between twenty-four to forty-eight hours.

⁴ Deaths inside four hours.

⁵ Deaths between forty minutes to sixty hours.

⁶ Deaths inside one hour.

A short series in which these two drugs were given subcutaneously showed decidedly more favorable results as compared to tartar emetic. Tartar emetic killed the 1 mouse in which it was injected in both 0.1 and 0.05 mg. dosage; it was sub-lethal when injected in 0.02 and 0.01 mg. dosage in each of 2 mice. The T. A. T. preparation was non-lethal in 5 animals (mice); 2 received 0.05 mg.,

2 received 0.08 mg. and 1 was given 0.1 mg. per gram of body weight. Likewise the S. A. T. preparation did not kill 5 mice in which it was injected subcutaneously: 2 were given 0.01 mg., 1 was given 0.05 mg., and 2 were given 0.1 mg. per gram of body weight. (Table II.)

TABLE II.—SUBCUTANEOUS INJECTIONS.

		Dose in mg. per gm. of body weight.					
		0.01	0.02	0.05	0.08	0.1	0.25
Tartar emetic	Injected	1	1	1	..	1	
	Died	0	0	1	..	1	
T. A. T.	Injected	2	2	1	
	Died	0	0	0	
S. A. T.	Injected	2	..	1	..	2	
	Died	0	..	0	..	0	

Summarizing our toxicity studies briefly, it appears that the S. A. T. preparation, though having the highest antimony content is the least toxic of the three antimony compounds, both intravenously and subcutaneously, though its safe intravenous dosage is equivalent to that of tartar emetic. The toxicity of the T. A. T. preparation stands between the two others, though again its safe intravenous dosage is equivalent to tartar emetic. In behalf of this latter drug (T. A. T.) it is to be said that its low solubility rendered it necessary to give to mice a larger bulk injection than was used in administering the other drugs, a technical difficulty, and a lethal factor not to be forgotten. Subcutaneously, both the T. A. T. and S. A. T. preparation are far less toxic than tartar emetic.

Figuring these results into terms of dosage for man, one finds that the safe dosage of 0.025 mg. per gram of body weight is the equivalent of a dosage of 1.7 gm. to a man of 150 pounds. This is exactly seventeen times more than what has been used as the maximum dosage in clinical cases, and by means of which most satisfactory therapeutic results have been obtained.

Dosage. In the preliminary report it was pointed out that on Dr. Abel's suggestion the dosage of these new drugs was to be judged by keeping it within the limitation, as to antimony content, as compared with tartar emetic, which we were then using successfully. We were using tartar emetic in 1 per cent strength and giving 10 cc as a maximum dose, *i. e.* 0.1 gm. of the drug. Antimony occurs in tartar emetic as 36.16 per cent of the whole. Finding the antimony content of T. A. T. and S. A. T. to closely approach that of tartar emetic, it was concluded to administer the new drugs in similar dosage to that already tried with tartar emetic, though feeling from Dr. Abel's statements that they would be less toxic, and less irritating.

T. A. T. The usual course pursued was to use T. A. T. in 25-cc dosage, it being prepared sterilized in ampules of this size. Its solubility being limited to less than $\frac{1}{2}$ of 1 per cent, this size injection

was necessary to obtain 0.1 of the drug. Later 20-cc ampules of an accurate 0.4 per cent solution were used, giving a dosage of 0.08 gm. This has uniformly proven to be a non-toxic, non-irritant injection in all clinical cases, and at the same time possessing a potentially high therapeutic value. At no time has there been seen any symptoms of intolerance such as we had been used to expect when tartar emetic was administered in maximum dosage, and in several patients who were intolerant to tartar emetic, or regularly developed bone aches, attacks of dyspnea, and coughing spells, after tartar emetic injection, were found to take this drug without the slightest inconvenience. (Cases III, V, VII, and IX.)

Constant urinalysis failed to demonstrate any kidney irritation, the same have been omitted from case protocols for sake of brevity, and likewise no evidence of irritant action on the vein walls at the site of injection has been observed.

Our toxicity studies on this drug have proved that the dosage used clinically is one-seventeenth of the safe dosage in experimental animals judged on body weight, and it does not seem necessary from a therapeutic standpoint to administer any larger amounts. This places the $\frac{C}{T}$ dose ratio, *i. e.*,

Curative dose, or dose sufficient to destroy all parasites

Toxic dose, or maximum dose which the patient can tolerate

well within the accepted limit, which to be of value, Ehrlich maintained, should be not greater than one-third.

S. A. T. With S. A. T. whose antimony content is slightly greater than that of tartar emetic, we again adhered to a similar maximum dosage of 0.1 gm. Its solubility being high, it has been used in both a large dilution of 20 cc of a 0.5 per cent solution, and also in the more concentrated form of 10 cc of a 1 per cent solution. It likewise has proven devoid of irritative effect locally as administered and has been borne by all patients without reaction suggestive of antimony intoxication.

Toxicity studies on this drug have shown that it is relatively more safe than either tartar emetic or T. A. T., and clinical observations have likewise left an impression that the patient receives it more kindly.

Administration. Intravenous injection has been the rule because of the violent irritant action which we had learnt to expect when tartar emetic was injected extra-venously. This intravenous administration has given uniformly excellent therapeutic results and without evident general, local, or vascular irritation.

Intravenously, either of the drugs should be given every second day to obtain prompt and successful results.

In 7 cases daily injections were given and received without evidence of intolerance and without symptoms of reaction. (Cases

I, II, III, IV, V, VI and VII.) In 1 patient (Case VI) weekly injections were given for a period of time, only to find the lesion remain almost stationary, and his subsequent healing seemed delayed, though evidencing no recrudescence. It has been a rule to start treatment with a fraction of the considered maximum dose of 0.1 gm., in using either drug. However, several patients (Cases IV, V and VII) were given this maximum dosage as their initial injection and no reactionary symptoms were manifested.

Although prompt healing was observed in all these cases, experience has shown that one is dealing with a very chronic infection, in fact oftentimes a lesion of many years duration; also recurrences are not rare and generally appear about the periphery of the healed lesion. These facts have emphasized the necessity of continuing treatment long after apparent healing by epithelialization has occurred, if one wishes a permanent cure, and we have advised all patients to receive at least 12 injections after his first healing has taken place. It has been interesting to note in some of our old patients that the rather marked and characteristic edema that frequently accompanies a granuloma of soft tissues will ultimately disappear entirely if treatment is persisted in.

In subsequent conversations with Dr. Abel, he assured me that subcutaneous injections in his experimental rats were without apparent irritant or suppurative action. On this authority we have started studies along this line which will be the subject of a future communication, using the drugs both subcutaneously and intramuscularly. If such prove possible, and our experience so far seems to point that they will, it would be a tremendous asset in antimony therapy. (See Case histories IV, VII and IX.¹)

CASE I.—R. F., a colored male, aged twenty-seven years, entered the Philadelphia General Hospital, August 5, 1922, complaining of large swelling of the scrotum. The onset was eighteen months ago as a small sore on the foreskin. This was painless, caused no discomfort but spread slowly with marked phimosis. A private physician gave him a "dorsal slit," and because of the accumulation of pus, the prepuce was likewise, at a later date, opened on the ventral surface. Following this, his entire external genitalia began to swell. He received a course of injections in the arm (most likely arsphenamin) but no improvement followed. Six months from the

¹ No local irritation was observed in the animals where injections were given subcutaneously. To date (May 1, 1924) 2 further patients have received 12 intramuscular (gluteal) injections of S. A. T. (2 cc of a 5 per cent solution). They have all been received without evidence of suppuration, and with but slight transient sensations of dull pain. Fourteen intramuscular injections of T. A. T. have been administered. The low solubility of this drug, necessitating greater bulk injections, is strongly against its intramuscular use. Two of these did suppurate, 1 given in the deltoid on the nineteenth day, the other (gluteal) on the thirty-third day; each received 12 cc of the solution and faulty technic in syringe sterilization (immersion in alcohol) might have played an important part.

onset of his trouble his scrotum was swollen to the present size; the penis disappeared into the swollen mass and a series of open lesions appeared on the skin of the scrotum. At no time has he suffered any marked discomfort or pain. Physical examination is negative except for genitalia. Scrotum presents a tumorous mass 8 inches in diameter. Entire surface is raw and covered with a granulating lesion and presents several sinuses through which urine has passed. Penis is completely lost in the tumor. In the right groin is a characteristic granulomatous area. Urinalysis and blood count were essentially normal.

Blood Wassermann. Negative.

August 9, 1922. Smear positive for granuloma organisms.

August 11, 1922. Culture positive for granuloma organisms.

The patient was placed upon intravenous injections of T. A. T. The drug was prepared in 25-cc glass ampules containing 0.4 per cent solution. His first injection consisted of a half ampule, which was increased so that by the fourth injection he was taking the full ampule dosage. This dose is equivalent to 0.1 per cent of the drug. Injection given on the following dates: August 8, 9, 10, 11, 13, 14, 15, 16, 17 and 18.

August 21, 1922. Lesions are today covered with epithelium and healed.

Swelling of the scrotum has not decreased in size, though it is very much softer. He has not at any time suffered any reaction to injections other than the local benefit observed in his lesions by rapid healing. A full-size dosage was administered on the following dates: August 29, 30, September 5, 6, 7 and 8.

September 11, 1922. Patient was this day changed from injection of the above drug to tartar emetic, 10 cc of a 1 per cent solution being given, which was repeated on September 13 and 16.

On November 15, a plastic operation was performed by the attending surgeon (Dr. Elwood Kirby). The thickened scrotal wall was for the greater part excised and the penis reconstructed with a skin covering. He received 17 further injections of tartar emetic and was discharged February 2, 1923, in a completely healed condition and remarkably improved.

He received 16 injections of T. A. T., totaling 1.41 gm. of the drug and obtained a complete healing of all open lesions.

CASE II.—J. S., a colored male, aged thirty-nine years, was admitted to the Philadelphia General Hospital June 19, 1922, complaining of sores in both groins of eight years' duration. Contracted disease while in the south, starting as a "chancroidal" sore in 1914 complicated with bilateral bubo. (Patient was admitted to this hospital in 1916 for lesions in both groins. He was treated by roentgen-ray exposures and healed in six months. About one

and a half years later groins again became the seat of open lesions which "he worried along with" until 1920 when a second admission to this hospital occurred and he was again treated by roentgen-ray and almost healed in ten weeks' time. Nine months ago the lesions again became active and spreading, and have continued to increase in size from that time to this his third admission at the above date.) The sores are now larger than they ever have been. There is pain on motion but no loss of weight. Examination is unimportant except for genitalia. In each groin is a sore 3 inches long, 1 inch wide. On the left this spreads down to the scrotal-thigh fold. It is covered with typical granulation tissue and devoid of exudate other than a moist mucus. There is no odor, nor undermining. The same process involves the under portion of the foreskin.

June 26, 1922. Blood Wassermann was negative. Spinal fluid Wassermann was negative. Smear negative for granuloma organisms.

June 20, 1922. On account of typical lesion and history, treatment started in spite of negative bacteriological findings. Patient was given 10 cc of 0.4 per cent solution T. A. T. intravenously. There was no reaction. Persistent pains in lesions were relieved immediately following the injection of the drug.

July 2, 1922. Patient given 20 cc of 0.4 per cent solution of T. A. T. intravenously. Edges of granuloma lesions drying up.

July 3, 1922. Given 20 cc 0.4 per cent solution T. A. T. intravenously. There is marked shrinkage in lesions; no pain since first injection. Owing to the limited supply of the drug, this patient received on July 4, 5, and 6, 10 cc of 1 per cent solution tartar emetic without pain or reaction.

July 7, 1922. Given 20 cc of T. A. T. intravenously. This dose was repeated on the following dates: July 9, 11, 14, 15, 16, 17 and 18. On this date the lesion on penis is flat, dry, nearly healed; groin lesions show marked epithelial proliferation and drying of lesions; complete absence of pain since first injection; in fact the lesions today are covered with epithelium, though the redundant watery proliferating nodules about the same have not disappeared but show marked shrinkage in size.

The above dosage of T. A. T. was given intravenously on the following dates: July 19, 20, 22, 24 and 25.

July 26, 1922. On account of disorderly conduct this patient was today discharged from the ward to the out-patient department. His lesions are practically healed, though he is to continue injections of tartar emetic at weekly intervals.

Final Note. September 15, 1923. This patient has been regular in attendance at the out-patient department and has remained completely healed to date. He received 16 injections of T. A. T. totaling 1.24 gm., plus 3 injections of tartar emetic, to a complete cure.

CASE III.—C. W., a colored male, aged twenty-three years, was admitted to the Philadelphia General Hospital July 22, 1922, complaining of sore on the penis. The present lesion is of seven years' duration; started as a soft painful sore on the prepuceal margin which was healed under local treatment in sixty days. It remained healed however only four or five months when it broke out again and extended along the shaft of the penis toward the body. It was again treated with local applications and apparently healed for a period of five months; again returned and continued as an open sore until the present time. (In 1917–1918 he received 10 injections of cacodylate of soda, and later he was given 8 injections of mercury and a series of intravenous injections of neosalvarsan in the arm. He has had no medical treatment during the past year.) Physical examination unimportant except for genital lesion. Beneath the glans penis is a large irregular area (an effort was made in 1919 to excise the growth but was unsuccessful and recurrence promptly appeared) of an old operative wound. Around this is redundant, hard, smooth, skin and approximal to this is an elevated nodular tender growth; its surface is covered with soft granulation tissue. There is marked induration of all the loose cellular tissue over the shaft of the penis about the lesion. The glans is not involved; the lesion seems to be quite painful to handling.

July 23, 1922. Urinalysis: essentially normal. Leukocytes, 8700; hemoglobin 54 per cent; red blood cells 5,340,000.

July 24, 1922. Blood Wassermann positive; smear and culture positive for granuloma organisms.

August 7, 1922. On account of the presence of a positive Wassermann, the patient was given 2 injections of neosalvarsan, also injections of mercury, and potassium iodid in increasing doses to date without any apparent improvement in his local condition. Today he was given 10 cc of 0.4 solution of T. A. T. intravenously.

August 8, 1922. Given 17 cc of 0.4 per cent solution T. A. T. intravenously.

August 9, 1922. Given 18 cc of 0.4 per cent solution T. A. T. intravenously.

August 10, 1922. Given 19 cc of 0.4 per cent solution T. A. T. intravenously.

On the following dates he was given 20 cc of 0.4 per cent solution T. A. T. intravenously: August 11, 13, 14, 15, 16, 17 and 18. (The pain in the lesion, which was rather severe, completely disappeared following the first injection and has been absent ever since.) On the last date the lesion is reported as being dry and rapidly healing and marked shrinkage in the heavy indurated tissue. The above dosage was repeated on August 19, 30 and 31.

September 1, 1922. There are still some moist areas in the lesion, though the anterior and posterior portion are greatly improved.

On the following dates 20 cc of 0.4 per cent solution T. A. T. was

given intravenously: September 1, 2, 5, 6, 7 and 8. It is to be noted that the patient has not suffered any reaction at any time from this drug; as his healing has been slow to date, it was thought wise to try him on tartar emetic.

September 11, 1922. Given 10 cc of 1 per cent solution tartar emetic intravenously.

September 12, 1922. Patient has a rather sharp reaction to the above injection with persistent pains in the long bones; some dysuria and cardiac palpitation.

September 13, 1922. Given second injection of 10 cc of 1 per cent solution tartar emetic intravenously.

September 14, 1922. Patient again suffered a reaction to the injection, more severe than on the prior dosage.

September 16, 1922. Patient given 10 cc of 1 per cent solution of tartar emetic intravenously; immediately suffered a violent reaction, coughing, vomiting, dizziness and rapid breathing.

Fearing further toxic reactions from tartar emetic, 20 cc of 0.4 per cent solution T. A. T. was given intravenously on September 23 and 27. There was no reaction.

October 2, 1922. Patient requested his discharge. Lesion on the penis has shown slow but progressive improvement. There are at present no raw areas and the lesion is completely covered with epithelium. There has been a decrease of about one-third in the heavy induration underlying the growth. Patient was discharged to the out-patient department for continuation of treatment.

COMMENT. He received at first 18 injections of T. A. T., totaling 1.556 gm. of the drug without the slightest reaction. He then received 3 injections of tartar emetic each of which was followed by increasingly alarming symptoms that demanded their cessation. He was then given 2 further injections of 20 cc each of 0.4 per cent solution T. A. T., totaling 0.16 gm. without any reaction whatsoever.

CASE IV.—W. G., male, colored, aged twenty-two years, was admitted to the Philadelphia General Hospital June 17, 1922, complaining of a sore in the right groin and a lesion on the penis. These are of two and a half years' duration and developed after circumcision for chancroid and the opening of a right inguinal bubo. Examination of the genitalia presented an old sore on the frenum which has remained since circumcision for chancroid (?) in 1919. In the right groin is a typical granuloma lesion 2 inches long by $\frac{3}{4}$ of an inch wide with redundant edges and no undermining.

June 19, 1922. Blood Wassermann is negative.

June 20 and 26, 1922. Smears negative for granuloma organisms.

June 21 and 27, 1922. Cultures negative for granuloma organisms.

June 30, 1922. Patient given 5 cc of 0.4 per cent solution T. A. T. subcutaneously over each shoulder blade. He suffered severe pain

from the time of the injection, and required a hypodermic of $\frac{1}{4}$ gr. morphia to control it.

July 2, 1922. Given 20 cc of 0.4 per cent solution of T. A. T. intravenously.

There was no reaction and pains in his lesions which had been severe from the time of his admission were immediately relieved.

July 3, 1922. Similar dosage given intravenously followed by marked shrinkage of the edges of his granuloma. Patient has had no more pains in his lesions. On account of the scarcity of the drug, this patient had to be changed to tartar emetic, which he received at two- to three-day intervals and was healed July 24.

September 15, 1922. This patient has been in regular attendance at the out-patient department and has remained healed to date.

COMMENT. He received 10 cc of 0.4 per cent solution T. A. T. subcutaneously; this caused pain. He was subsequently given two doses of 20 cc each of 0.4 per cent solution T. A. T. intravenously with marked relief of pain in his lesions and improvement in their condition, followed by tartar emetic to a permanent cure.

CASE V.—W. F.,¹ male, colored, aged thirty-five years, was readmitted August 23, 1922, with a recurrence of the anal lesion that appeared four weeks after leaving the hospital; the recurrence occurring principally about the periphery of the old lesion and extending forward to the perineum and to the scrotal attachment. He was placed again on tartar emetic treatment, being given 10 cc of a 1 per cent solution on alternate days. He seemed now particularly susceptible to tartar emetic and after each injection he was laid up the following day with bone pains and always had a severe coughing spell of ten to twenty minutes' duration immediately following the injection.

September 18, 1922. Patient was given a full dose of T. A. T. (0.1 gm.) without any reaction whatsoever. This dosage was repeated on the following dates: September 27, 29, 30, 31, October 5, 6, 11, 13 and 16. There was no recurrence of his intolerance to antimony as seen when tartar emetic was used and each dose was taken without symptoms of any kind.

October 24, 1922. The patient reports anal lesion is completely healed. Patient discharged to a hospital physician for observation.

February 15, 1923. Patient left the hospital physician today. He has remained healed from the time of his last injection to the present date, now four months past. He received 10 injections of T. A. T., totaling 1.0 gm. of the drug and received the same without the reactions that had caused tartar emetic to be almost prohibitive.

¹ This patient was Case VI of our published series in Surgery, Gynecology and Obstetrics (June 1, 1922). He was on that admission discharged, April 23, 1922, for further treatment in the out-patient department, which he failed to follow.

CASE VI.—C. D., A. 3972, male, colored, aged twenty-six years, entered the out-patient department University of Pennsylvania Hospital, May 8, 1923, with an ulcer in the coronal sulcus on the right, of nine days' duration. Dark field was negative; repeated again the following day and again found to be negative. Wassermann was likewise negative. The lesion was treated as a chancroid and patient disappeared from observation on May 25 practically healed. Wassermann taken under date of last visit was strongly positive.

Returned to out-patient department September 1, 1923, with a triangular area measuring 4 x 3 x 3 cm. in the midline in the pubic hair region that was covered with a scab, and practically painless, and overlying a deep-seated induration which extended downward to the right lateral side of shaft of penis, and to the region of the external inguinal ring. He gave a history of having had an abscess at this situation, which was opened, and had likewise been given some injections of salvarsan before returning to us.

September 5, 1923. Smear positive for granuloma organisms.

September 8, 1923. Given 15 cc of 0.5 per cent solution S. A. T. intravenously.

September 12, 1923. Given 20 cc of 0.5 per cent solution S. A. T. intravenously.

September 15, 1923. Given 20 cc of 0.5 per cent solution S. A. T. intravenously. Lesion shows healing about periphery.

September 19, 1923. Given 20 cc of 0.5 per cent solution S. A. T. intravenously.

September 24, 1923. Given 20 cc of 0.5 per cent solution S. A. T. intravenously.

Deep seated induration has practically disappeared and lesion is dry, painless, and covered with a scab which is easily removed, showing a surface three-fourths covered with epithelium; remainder with soft bleeding granulation tissue.

The patient was given the above dosage on the following dates: September 29, October 5, 13, 27, November 3, 26 and December 1. These last injections were given at weekly or greater intervals, and there was a cessation of the rapid healing and though progress was obtained, it was not as consistent as when injections were given at shorter intervals. Feeling that it might possibly be due to his syphilitic infection, the patient was given during the months of December and January weekly injections of neosalvarsan, and on the following dates the patient was given 20 cc of 0.5 per cent solution S. A. T. intravenously: January 25, 26, 31, February 1, 2, 6, 9 and 14. The patient was lost to observation following this last injection; the lesion is recorded as healed on the visit of February 2, 1924.

CASE VII.—A. H., A. 4974, aged thirty-eight years, a colored male, was admitted to out-patient department February 12, 1924,

complaining of sore on penis of ten days' duration. Started like a small boil. A few days after onset, patient picked top off and scab formed. The scab has been rubbed off several times. The lesion was at the base of penis, on dorsal surface, is perfectly circular and 2 cm. in diameter, with a small papule at one edge. The lesion was covered with a crust-like formation. This crust was removed and smear made, which was positive for granuloma organisms. Second papule is just breaking at pubic hair margin in right groin.

February 13, 1924. Given 20 cc of 0.5 per cent solution S. A. T. intravenously.

February 15, 1924. No reaction. Given 20 cc of 0.5 per cent solution S. A. T. intravenously.

February 18, 1924. Given 3 cc of 1 per cent solution tartar emetic intravenously. Healing has started with epithelial proliferation about edge.

March 20, 1924. Because of the scarcity of the new drug, patient has been given tartar emetic in 0.05 to 0.1 gm. dosage on the following dates: February 21, 25, 28 and March 3, 6, 13, 14 and 18 and today. These treatments were all given in the dispensary and patient recounts that though no disagreeable symptoms have followed, rheumatoid pains in the shoulders have been constantly present for twenty-four hours after injection. Lesion today is healed except for a slight portion about periphery that persists in scabbing over. Lesion in pubic hair region has disappeared completely.

March 21, 1924. Given 10 cc of 0.5 per cent solution S. A. T. in right gluteus and 10 cc intravenously. Developed slight coughing spell of fifteen minutes' duration, without other symptoms. This is the first symptom of this kind observed with this drug and possibly due to giving drug the day following tartar emetic.

March 24, 1924. Given 10 cc of 0.5 per cent solution S. A. T. in left gluteus and 10 cc intravenously. There was no reaction. The previous intramuscular injection caused no discomfort.

March 27, 1924. Given 20 cc of 0.5 per cent solution S. A. T. intravenously. Gluteal muscles sore to deep pressure; no pain; no lump. Vomited after leaving dispensary.

April 1, 1924. Given 20 cc of 0.5 per cent solution S. A. T. intravenously. Gluteal muscle less sore. He had a sharp "nitritoid" reaction. (*N. B.*—These last 3 S. A. T. injections are from a new lot. Another dose given to a new patient likewise caused reaction: Solution slightly colored and undoubtedly not pure.) Lesion completely healed.

April 8, 1924. Given 10 cc of 0.4 per cent solution T. A. T., no reaction.

April 11, 1924. Given 20 cc of 0.4 per cent solution T. A. T., no reaction.

April 15, 1924. Given 20 cc of 0.4 per cent solution T. A. T. no reaction.

April 22, 1924. Given 20 cc of 0.4 per cent solution T. A. T., no reaction. Gluteal muscles normal.

NOTE.—October 8, 1924. Patient has taken 28 full doses of T. A. T. since the above date, all devoid of any reaction.

CASE VIII.—McK. T., A. 3358, a colored male, aged twenty-one years, entered the dispensary November 28, 1922. Developed a small sore on glans penis with swelling of prepuce two years ago, which has remained since as a painless lesion. Recently a second open sore appeared on under side of prepuse, which is raw, red and covered with granulation tissue. There is no undermining; no discharge; practically no pain. There is heavy chronic edema of the distal half of penile skin, and the prepuce is rendered irretractible by the same.

November 29, 1922. Smear negative for granuloma organisms. Urine shows trace of albumin; occasional red blood cell and white blood cell.

December 2, 1922. Smear again negative for granuloma organisms.

December 9, 1922. Smear is positive for granuloma organisms. Given 7 cc of 1 per cent solution S. A. T. intravenously.

December 11, 1922. Given 8 cc of 1 per cent solution S. A. T. intravenously.

December 13, 1922. Given 9 cc of 1 per cent solution S. A. T. intravenously. Sore is rapidly covering with epithelium.

December 15, 1922. Given 10 cc of 1 per cent solution S. A. T. intravenously.

December 17, 1922. Given 15 cc of 0.4 per cent solution T. A. T. intravenously.

December 19, 1922. Given 15 cc of 0.4 per cent solution T. A. T. intravenously.

December 22, 1922. Given 20 cc of 0.4 per cent solution T. A. T. intravenously. Lesions are now healed; prepuce retractible.

Patient was advised to continue treatment but was lost to further observation. He received 4 injections of S. A. T., totalling 0.24 gm. of drug, and 3 injections of T. A. T., totaling 0.2 gm. of drug.

CASE IX.—W. R. was No. 3 of the series of cases reported in the *Journal of Urology* for June 9, 1923. At that time he gained a complete healing under sodium antimony thioglycollate and tartar emetic, being discharged on January 31, 1922 to continue his injections in the out-patient department, which he neglected to do owing to the fact that shortly after his discharge he was arrested and placed in jail. On his discharge from jail, on April 1, 1922, he already noticed a recurrence of his granuloma and was readmitted to the hospital on April 8, 1922, desperately ill with lobar pneumonia. His recovery was prompt, and on April 25, 1922 he was transferred

to the genito-urinary service for treatment of the recurrence of his granuloma. The growth appeared as a conglomerate roseola about the periphery of his primary lesion, the center of which is still covered with healthy epithelium. Smears taken at the time of his transfer on April 25 were positive for granuloma organisms.

During this patient's previous admission he had shown marked reaction after each injection of tartar emetic, but had taken S. A. T. without the slightest trouble.

May 8, 1922. Given $2\frac{1}{2}$ cc of 0.4 per cent solution of T. A. T. intravenously; 5 cc of the same solution was injected subdermally. There was no reaction to either the intravenous or subdermal injection of the drug.

May 10, 1922. Given 5 cc of 0.4 per cent solution T. A. T. intravenously.

May 12, 1922. Given 10 cc of 0.4 per cent solution of T. A. T. intravenously. Lesion is beginning to heal nicely.

May 14, 1922. Given 20 cc of 0.4 per cent solution T. A. T. intravenously. Marked progress in healing. This dosage was repeated on May 16, 18, 22, 24, 28, June 1, 3, 5, 7 and 9.

June 10, 1922. All lesions are now completely healed. This dosage was continued on alternate days until June 29, 1922 when he was discharged to the out-patient department with advice to continue his injections once per week.

He received 23 injections of T. A. T., totaling 1.61 gm. with complete healing of his lesions. Tolerance to the drug was perfect and at no time were reactions obtained that had made previous tartar emetic medication perilous.¹

CASE X.—W. MacL., A 3624, male, colored, aged twenty-six years, entered the dispensary of the University of Pennsylvania Hospital, February 7, 1923. He was circumcised two years ago, at which time he had an ulcer on right side of prepuce; circumcision scar refused to heal and ulceration has persisted to present time. Lesion appears as a narrow granulomatous sore along the line of scar of circumcision under which is a heavy indurated edematous condition of the surrounding skin. Smear is positive for granuloma organisms. Wassermann, negative.

February 7, 1923. Intravenous administration of 6 cc of 0.4 per cent solution of T. A. T.

February 17, 1923. Intravenous administration of 10 cc of 1 per cent solution S. A. T.

February 20, 1923. Intravenous administration of 10 cc of 1 per cent solution of S. A. T. Lesions are completely healed over. This dose of 10 cc of 1 per cent solution of S. A. T. was repeated on the following dates: February 20, 26, March 1, 5, 13, 20 and April 9.

¹ Colored drawing of this lesion is to be found in Cabot's Urology, 2d edition.

The lesion has healed completely; edema markedly improved. Patient lost to observation. This patient received 9 injections intravenously of S. A. T., totaling 0.9 gm. of the drug without reaction; as likewise 1 injection of T. A. T.

CASE XI.—T. L., A 4437, male, white, aged sixty-three years, was admitted to the University of Pennsylvania Hospital September 25, 1923. Condition of inoperable carcinoma of the bladder involving two-thirds of the vesical wall, causing urgency and frequency of urination with marked hematuria. The drug was administered to observe effect. Patient kept in hospital to receive deep roentgenotherapy.

He received, at every two- to three-day intervals, a total of 13 injections of T. A. T., totalling 0.996 gm. of the drug. There was no visible improvement in the patient's condition; there was no reaction to the drug; no intolerance or accumulative effect seen, and no local reaction at site of venous puncture. This was purely a negative study and is reported as a case showing toleration to the drug.

CASE XII.—P. W., A. 3919, male, white, aged fifty-two years, entered the University of Pennsylvania Hospital April 23, 1923. Patient's history recorded British Army service in India and Egypt, during which he had an attack of cystitis associated with hematuria, with which a number of the men in his command likewise suffered. A most unusual cystoscopic picture was thought to be bilharziasis. The most painstaking and repeated urine examinations failed to demonstrate ova, and were likewise negative for the tubercle bacillus. Catheterized kidney specimens showed clear urine, and a differential functional test gave bilaterally equal and normal function.

The following injections were given empirically:

May 7, 1923. Given 7 cc of 1 per cent solution of S. A. T. intravenously.

May 10, 1923. Given 8 cc of 1 per cent solution of S. A. T. intravenously. Each of these injections seemed to cause a flare-up of his cystitic condition with excessive outpouring of a mucopurulent urine. Injections were delayed while further diagnostic laboratory researches were made. These proved again negative, as likewise biopsy of vesical lesion.

May 22, 1923. Given 7 cc of 1 per cent solution S. A. T. intravenously.

May 24, 1923. Given 8 cc of 1 per cent solution S. A. T. intravenously.

May 27, 1923. Given 8 cc of 1 per cent solution S. A. T. intravenously.

June 2, 1923. Given 20 cc of 0.5 per cent solution S. A. T. intravenously. This dosage was repeated on the following dates: June 7, 11, 16, 21, 28 and July 9. On the continuation of treatment no

further reactions were observed and at the end the clinical picture appeared practically unchanged. This is reported as a case showing toleration of the drug. He received 12 injections of S. A. T., totaling 1.08 gm. of the drug.

EXTRANEOUS CASES. Besides the above cited patients (Cases XI and XII) in which one of the drugs was administered for conditions other than granuloma, the S. A. T. preparation has been given intravenously to 13 other patients suffering from various infections, in order to observe its therapeutic value and tolerance. Without reporting these cases in full, it is worthy to note that 3 patients received 1 dose; 1 patient received 2 doses; 2 patients received 3 doses; 2 patients received 4 doses; 3 patients received 5 doses and 1 patient received 6 doses and another 12 doses. This is a total of 52 doses, all given intravenously. Three patients were given the full dosage of 20 cc of a 0.5 per cent solution of S. A. T. as their initial injection. They were all received without evidence of toxicity or intolerance. Four were ward patients and their urine was watched for indications of renal irritation without observing such to occur.

Discussion. Of 10 patients suffering with granuloma inguinale herein reported, 5 received the T. A. T. preparation, 4 of whom were completely healed. (Cases I, II, III and V). The fifth patient (Case IV) had to forego further treatment after 3 injections because of the scarcity of the drug to hand at the time: his healing was completed with tartar emetic. Three of the 4 cured patients (Cases I, II and III), during part of their treatment, received daily maximum dosages of 0.1 gm. over a period of four, five and six days without symptoms of toxicity or intolerance. One of them (Case III) who had received T. A. T. in such concentration without the slightest difficulty, when subsequently given tartar emetic, suffered alarming reactionary symptoms, and then again took T. A. T. without the slightest trouble. This intolerance for tartar emetic and complete toleration for T. A. T. was again observed in Cases V and IX. The complete relief of pain in the lesion immediately following the first administration of the drug was observed in 3 patients (Cases II, III and IV). One patient, and he one of the cases that was intolerant to tartar emetic (Case V), was started on the maximum dosage of 0.1 gm. with the first injection and experienced no ill-effects whatsoever. Healing in all these cases was certainly as rapid as we were accustomed to see under tartar emetic therapy, while the sense of security rapidly formed after brief experience with the drug, due to the absence of reactions observed in certain patients after tartar emetic had been administered, made one feel doubly grateful for its efficacy at all.

Two patients with granuloma inguinale were treated with the S. A. T. preparation: both were healed. (Cases VI and VII.) The first received prompt therapeutic results with a remarkable disap-

pearance of the deep-seated induration often accompanying these lesions, until the intervals between injections were allowed to lapse to weekly periods, when a definite slowing up of the healing process was observed. Subsequently, a more active therapy established the cure. During his treatment, full daily doses of 0.1 gm. were given for three consecutive days without symptoms of intolerance or toxicity. The second patient likewise handled the drug without the slightest trouble, except on one occasion when it was given the day following an administration of tartar emetic, a short coughing spell of fifteen minutes' duration ensued, without change in pulse-rate or volume or other untoward symptoms, and on the third and fourth administration of an experimental combination of this drug he showed antimony intoxication. He was then placed on T. A. T. and has taken 28 full doses to date without the slightest trouble. Tartar emetic was given to him for a short while and he regularly experienced rheumatoid pains following each injection, symptoms that were absent when taking S. A. T. He also received the maximum of 0.1 gm. on his initial dose.

The therapeutic value of this S. A. T. preparation seems equal to that of the T. A. T. drug. It is difficult to draw comparisons in so few patients, especially so when the evidence is devoid of disagreeable circumstances and is to be based only on the rapidity of healing, and that in patients whose lesions vary markedly in extent.

Three patients were given injections of both drugs for comparative results. All were cured. (Cases VIII, IX and X.) The first of these was given 4 injections of S. A. T. at second-day intervals, followed by 3 injections of T. A. T. Prompt healing ensued, and no untoward symptoms were experienced. The second had been given S. A. T. at a previous admission. He likewise developed a marked idiosyncrasy to tartar emetic and begged not to be given it. He was given 23 injections of T. A. T. on alternate days to a complete healing. His toleration of the drug was perfect. The third patient was first given 1 injection of T. A. T., and then 9 injections of S. A. T. Healing was established without the slightest reaction to either drug. This comparison allows of no conclusions.

Two further patients are reported who did not have granuloma inguinale; 1 received 13 intravenous injections of T. A. T., while the other was given 12 injections of S. A. T., and in neither was there any evidence of antimony intolerance.

Summary. There have been treated 10 cases of granuloma inguinale: 9 have been cured by these drugs alone, while the tenth was cured with tartar emetic during a period of scarcity of the new compounds. The T. A. T. preparation has been administered intravenously 102 times: it has never given the slightest evidence of toxicity, and has been productive of a cure in 5 patients suffering with granuloma inguinale. A maximum dosage of 0.1 gm. has been adhered to. The S. A. T. preparation has been injected intraven-

ously 92 times, to a similar maximum dosage, and excepting the reactions recorded and explained in Case VII, it likewise has been borne without symptoms of antimony intoxication. It has cured the 2 patients in which it was used. Two further cases were cured by the administration of both drugs. Five patients showing symptoms of intolerance to tartar emetic, have taken one or the other of the drugs with the complete absence of such symptoms. Five patients have been given the considered maximum dosage as their initial dose, and have borne the same without any symptoms. To anyone who has used tartar emetic intravenously at all extensively, such successful results, as obtained by these drugs, will come as a hopeful advance in therapy.

Conclusions. 1. There are presented two new synthetic antimony compounds for intravenous administration.

2. Studies on animals show them to be of slightly lower toxicity than tartar emetic, while clinically they have failed to show any evidence of antimony poisoning so often observed in using tartar emetic.

3. Clinically they have evidenced no toxicity in the dosages advised, while 5 patients intolerant to tartar emetic have taken these drugs without reactions.

4. Neither of the two new drugs have shown any irritative effect at the site of intravenous injections.

5. Ten cases of granuloma inguinale are reported. Prompt, and complete healing, with evident cure, has been accomplished in 9 of them by the use of these new drugs.

6. Immediate relief of pain following the initial injection has been a remarkable manifestation in 3 of the patients.

7. The value of these drugs in other infectious conditions, where tartar emetic has proven efficacious may be expected.

8. Both preparations have been given successfully intramuscularly, though one is to be preferred.

9. As antimony belongs in that chemical group that embraces arsenic, mercury and bismuth, the possible value of these new drugs in syphilis might be expected, and is at present being studied.

Final Note. Antimony is rapidly receiving well-deserved attention as a drug of high therapeutic value when given intravenously for numerous diseases, especially those of protozoan origin and those oftentimes grouped as tropical diseases. At the Ranaghat Hospital (India) 8000 intravenous injections of the salts of antimony were given in the year 1921.¹

Reference to Abel and Roundtree's articles gives one a beautiful summary of the subject as applied to trypanosome and allied infections. Faber and Schussler in concluding their article on Leishmaniasis say: "Antimony is probably a true specific. It is still

¹ Mission Hospital, August, 1922, p. 211.

most commonly used as tartar emetic, but without doubt research will discover new combinations that are more effective and less toxic." With this in mind a bibliography is appended of recent literature concerning antimony therapy in an attempt to point out the possible conditions in which these two new synthetic drugs may gain a field of usefulness.

REFERENCES.

- Abel and Rowntree: Jour. Pharm. and Exper. Therap., 1910, 2, 101.
 Abel and Rowntree: Jour. Pharm. and Exper. Therap., 1911, 2, 501.
 Abraham: Indian Med. Gaz., 1923, 58, 479.
 Aragao and Vianna: Mem. do Inst. Oswaldo Cruz, 1912, 4, 211.
 Aragao: Brazil-med., 1919, 32, 74.
 Aragao: New Orleans Med. and Surg. Jour., 1917, 70, 369.
 Beeson: Arch. Dermat. and Syph., 1922, 6, 342.
 Benjamin: Nederl. Tijdschr. v. Verlosk. en Gynaec., 1921, 1, 25.
 Brahmachari: Calcutta Med. Jour., 1923, 17, 1.
 Brahmachari: Calcutta Med. Jour., 1923, 18, 481.
 Campbell: Jour. Am. Med. Assn., 1921, 76, 648.
 Castellani and Chalmers: Tropical Medicine, 3d edition, p. 2192.
 Cawson: Jour. Trop. Med. and Hyg., 1921, 24, 267.
 Cawson: Lancet, 1921, 2, 1049.
 Cawson: Jour. Trop. Med. and Hyg., 1922, 25, 126.
 Chopra: Indian Med. Gaz., 1923, 58, 1.
 Christiansen and Norton: Jour. Lab. and Clin. Med., October, 1923.
 Christopherson: Lancet, 1921, 1, 522.
 Christopherson: Brit. Med. Jour., 1920, 1, 854.
 Christopherson: Brit. Med. Jour., 1923, 2, 1254.
 Claasen: Ohio State Med. Jour., 1922, 18, 685.
 Crichlow: Jour. Trop. Med. and Hyg., 1921, 24, 74.
 Cummings: Brit. Med. Jour., 1920, 2, 3125.
 Cuthbert: Brit. Jour. Dermat., 1920, 33, 44.
 Diamantis: Jour. d. urol., 1923, 16, 471.
 Donovan: Indian Med. Gaz., 1905, 15, 414.
 Doyle: Indian Med. Gaz., 1920, 55, 410.
 Faber and Schussler: Jour. Am. Med. Assn., 1923, 80, 93.
 Fuentes and Estape: Ann. d. la Facul. de med., Montevideo, 1923, 8, 1005.
 Friedländer: California State Jour. Med., 1913, 11, 162.
 Goodman: Arch. Dermat. and Syph., 1920, 1, 151.
 Goodman: Jour. Am. Med. Assn., 1922, 79, 815.
 Grieg: Indian Jour. Med. Res., 1918, 5, 394.
 Guidon: Jour. Cutan. Dis., 1913, 31, 236.
 Guilian: Porto Rico Med. Assn. Bull., 1921, 15, 170.
 Hoffman: München. med. Wehnschr., 1920, 67, 159.
 Korns: China Med. Jour., 1921, 35, 564.
 Lambert: Jour. Am. Med. Assn., 1923, 80, 986.
 Lasbrey and Coleman: Brit. Med. Jour., 1921, 1, 299.
 Libby: China Med. Jour., 1923, 37, 158.
 Low and O'Driscoll: Lancet, 1921, 1, 221.
 Lowe and Neuham: Brit. Med. Jour., 1916, 1, 387.
 Lynch: Jour. Am. Med. Assn., 1921, 77, 925.
 Lynch: South. Med. Jour., 1922, 15, 688.
 McDonagh: Jour. Trop. Med. and Hyg., 1923, 26, 119.
 Maplestone: Ann. Trop. Med. and Parasitol., 1921, 15, 413.
 Morrissey: Jour. Tennessee Med. Assn., 1922, 15, 105.
 Napier: Indian Med. Gaz., 1923, 58, 578.
 Napier: Indian Med. Gaz., 1921, 56, 401.
 Pardo: Jour. Cutan. Dis., 1918, 36, 206.
 Parounagian and Goodman: Arch. Dermat. and Syph., 1922, 5, 597.
 Quintini: Gaceta med. de Caracas, 1921, 28, 56.
 Randall: Int. Jour. Surg., 1922, 35, 21.

- Randall: *Pennsylvania Med. Jour.*, 1922, 25, 593.
 Randall: *Jour. Urol.*, 1921, 5, 539.
 Randall: *Surg., Gynec. and Obst.*, 1922, 34, 717.
 Randall: *Jour. Urol.*, 1923, 9, 491.
 Ravaut: *Bull. de la Soc. méd. des hôp. de Paris*, 1921, 45, 865.
 Reed and Wolf: *New Orleans Med. and Surg. Jour.*, 1921, 74, 25.
 Reguzis: *Jour. Am. Med. Assn.*, 1923, 81, 60.
 Ross: *Virginia Med. Month.*, 1922, 48, 579.
 Sen Gupta: *Indian Med. Gaz.*, 1921, 5, 13.
 Shattock: *Boston Med. and Surg. Jour.*, 1923, 88, 530.
 Sinton: *Ann. Trop. Med. and Parasitol.*, 1921, 15, 107.
 Smith: *Brit. Med. Jour.*, 1908, 1, 488.
 Smith: *Arch. Dermat. and Syph.*, 1922, 5, 69.
 Spencer: *Jour. Am. Med. Assn.*, 1921, 76, 1494.
 Summons and Irving: *Med. Jour. Australia*, 1921, 5, 83.
 Symmers and Frost: *Jour. Am. Med. Assn.*, 1921, 74, 1304.
 Talbot and Lyon: *Am. Jour. Dis. Child.*, 1918, 16, 154.
 Walker: *Jour. Med. Res.*, 1918, 37, 427.
 Weinberg: *Jour. Urol.*, 1923, 9, 505.
 Ziemann: *Deutsch. med. Wehnschr.*, 1924, 50, 136.

EXPERIMENTAL BILIARY DRAINAGE IN THE DOG.

A PRELIMINARY NOTE.

BY A. WINKELSTEIN, M.D.,

AND

P. W. ASCHNER, M.D.,

NEW YORK.

(From the Surgical Laboratories of the College of Physicians and Surgeons,
Columbia University.)

CONFLICTING results have been obtained by experiments carried out on dogs to substantiate Meltzer's theory of contrary innervation between the gall-bladder and the sphincter of Oddi,¹ and Lyon's clinical application thereof.² These studies have chiefly concerned the question of the contractility of the gall-bladder, alone or in relation to the action of the sphincter of Oddi. They were usually conducted on dogs under the influence of depressant drugs or general anesthetics, with the abdomen open and the duodenum incised so as to expose the papilla of Vater.

In the course of a series of experiments performed under similar conditions (results to be published) we could not demonstrate contraction of the gall-bladder nor evidence of the law of contrary innervation. Interesting observations were made, however, on

¹ Meltzer, S. J.: *AM. JOUR. MED. SCI.*, 1917, 153, 469.

² Lyon, B. B. V.: *Jour. Am. Med. Assn.*, 1919, 73, 980.

the pressure factors concerned in the biliary flow. Appreciating the many unphysiological conditions present in this type of experimentation an effort was made, as described below, to imitate as closely as possible the circumstances existing when the Meltzer-Lyon test is carried out in the human.

Under ether anesthesia a median laparotomy was performed. Through a small opening in the anterior wall of the stomach, near the greater curvature, well away from the antrum, a narrow soft tube was passed and guided through the pylorus into the duodenum and upper jejunum. Small fenestra were made in the tube at the site of the papilla of Vater. The position of the tube was made secure by a double flange on it which was brought out through a small stab wound to the left of the primary wound. The stomach wall about the tube was likewise fastened to the parietes. With a small syringe and hypodermic needle, 2 cc of bile were withdrawn from the gall-bladder and replaced by an equal amount of dye (0.5 per cent methylene blue).

If at this point the duodenum was lavaged through the tube with warm 25 per cent magnesium sulphate solution, only light brown, bile stained fluid could be recovered, without a trace of dye. When the abdominal wound was closed by suture and this test repeated, the same result was obtained.

Further observations were made on the following day, the dogs having recovered from the effects of the anesthesia. In one animal, still fasting nineteen hours after operation, lavage of the duodenum with the magnesium sulphate solution yielded only yellow-brown bile. Five hours later, twenty-four hours after operation, the dog was fed some bread and water. Half an hour after feeding, the duodenal tube was aspirated and dark blue-dyed bile was recovered (gall-bladder bile). The following day, forty-six hours after operation, lavage with magnesium sulphate yielded fluid well stained by the dye. No dye was subsequently recovered from the duodenum of this dog. At autopsy one week after operation, the gall-bladder and ducts were found free of adhesions and no dye was present in the gall-bladder bile. It seems probable that the gall-bladder had been emptied of the original dyed bile within a period of forty-eight to seventy-two hours.

A second animal, examined twenty hours after operation, yielded 3 cc of dark brown bile upon aspiration of the duodenal tube. Instillation of magnesium sulphate solution yielded 15 cc of deeply blue-dyed fluid after five minutes, followed by yellow-brown fluid free of dye. No dye was subsequently recovered from this animal. At autopsy, five days after operation, the gall-bladder and ducts were normal. About 10 cc of brown bile, without dye, was found in the gall-bladder. Here again it seems probable that the organ had been emptied within a period of forty-eight hours.

A third animal, examined sixteen hours after operation, and still fasting, yielded 5 cc of brown bile upon aspiration. Lavage with warm water yielded only light yellow stained fluid. Lavage with magnesium sulphate solution yielded deeply dyed fluid for ten minutes, followed by light yellow-brown fluid containing no dye. In subsequent tests upon this dog we failed to recover any dye. Autopsy a week after operation showed no dye in the gall-bladder bile. The gall-bladder and ducts were normal. It seemed that the organ had been emptied within twenty-four hours.

Conclusions. From the above experimental observations, it may be concluded that following the introduction of warm 25 per cent magnesium sulphate into the duodenum of the dog, bile from the gall-bladder entered the duodenum. From other studies which have been made by the authors there is evidence that magnesium sulphate does this by inducing an adequate degree of relaxation of the sphincter of Oddi. Proof of Meltzer's theory of contrary innervation was not obtained. In fact, it is our belief that the assumption of this theory is not necessary to explain the mechanism of the biliary flow. Our conception of this mechanism together with studies on substances other than magnesium sulphate will form the basis of further communications.

REVIEWS.

BASAL METABOLISM IN HEALTH AND DISEASE. By EUGENE F. DU BOIS, M.D., Medical Director, Russell Sage Institute of Pathology; Associate Professor of Medicine, Cornell University Medical College. Pp. 372; 79 illustrations. Philadelphia: Lea & Febiger, 1924.

THERE is probably no one in this country better qualified to write on the subject of basal metabolism than Du Bois who, for years, has been studying the subject experimentally and clinically. Indeed his experimental studies are as important fundamentally as any that have been produced by any authority. In addition to Du Bois's qualifications on the experimental side of the subject, he has for some years been interested in clinical experimental studies which have been of tremendous value in elucidating the problems that have arisen as a result of his experimental work. For these reasons he is well qualified to prepare a monograph on basal metabolism.

The book is divided into two main sections, the first dealing with metabolism in health, the second with metabolism in disease. Metabolism in health deals with metabolism of the carbohydrate, fat and protein molecules, the general principles of respiration apparatus, methods of calculation, normal basal metabolism, estimation of the surface area of the body and so on: a most complete exposition of the subject. Metabolism in disease, the second portion of the book deals with metabolism in practically all types of disease, and shows explicitly, discussing in detail the several diseases, that the estimation of the basal metabolism as a clinical test is of value only in certain types of disease. Lastly, he discusses in a very brief chapter the effect of drugs on basal metabolism.

From the qualifications that Doctor Du Bois has one would expect a valuable presentation. In going over the book carefully the reviewer is in no way disappointed and his expectations were fully realized.

THE AVALANCHE. By ERNEST POOLE. Pp. 344. New York: The Macmillan Company, 1924.

THIS work of Poole is a psychological work in which the hero, a young doctor, performs near-miracles with patients who are on the

brink of insanity. He restores them to mental health by what seems a blend of mesmerism, hypnotism, animal magnetism, faith healing, the methods of Coué, the theories of Freud, and the maxims of William James, combined occasionally with a little morphin. It is rather a pity that his mode of procedure is not given more in detail as it was so singularly successful.

His life, however, is brief, for he unfortunately marries a very able and worldly young woman who attempts to launch him on a career of practical and spectacular success by a system of camouflaged advertising. He succumbs to a weak heart and the strain on his feelings of such mismating and dies in the sympathetic company of a Hindu philosopher.

Mr. Poole is an accomplished writer, and his analysis and presentation of character are finely done, but the prominent aspect of the novel is that the hero, who is supposed to be a wonderfully admirable and gifted person (as he would of course have to be to effect his miraculous cures), appears to be fundamentally of such a visionary, credulous and vague mind as to discredit the presumption that he would have been able under the happiest circumstances to contribute much to the progress of science. It is probable that the men who are to make the great discoveries in his chosen field which the future is undoubtedly to bring must have clearer heads and be of tougher mental fiber. U.

MEDICAL QUOTATIONS FROM ENGLISH PROSE. By JOHN H. LINDSEY, M.D. Pp. 298; 8 illustrations. Boston: Richard G. Badger, 1924.

THE medical quotations that Lindsey has selected for his book come from the works of nine well known writers, some of whom were physicians and some were not, but all of whom have been interested in the subject of medicine. He has coned the works of these English writers carefully and has collected practically everything they have to say about the subject of health. The most extensive collection are from the diary of Samuel Pepys. In fact they include almost a half of the book, and as usual with this entertaining writer the quotations are trite and interesting. It will well repay the student of literary medicine to go over the book and to read the various interesting quotations. M.

BASAL METABOLISM. By JOHN T. KING, JR., M.D. Pp. 118; 14 illustrations. Baltimore: Williams & Wilkins Co., 1924.

THE ever-increasing interest in basal metabolism as a result of the application to diseased states of the experimental studies of Du Bois,

upon the metabolism of the normal individual, has made necessary a text-book such as the present one that Doctor King now presents to the medical profession. The book is well balanced, the subject matter is clearly presented and is critically selected. The limits of basal metabolic studies are well brought out as are the important clinical data derived from the method. A large series of tables and a most excellent bibliography add considerably to the value of the work. M.

DISEASE in CAPTIVE WILD MAMMALS AND BIRDS. By HERBERT FOX, M.D., Pathologist to the Zoölogical Society of Philadelphia, Director of the William Pepper Clinical Laboratory, University of Pennsylvania; with a foreword by CHARLES B. PENROSE, M.D., President of the Zoölogical Society of Philadelphia. Pp. 665; with 28 analytical tables and 87 illustrations. Philadelphia, London and Chicago: J. B. Lippincott Company, 1924.

THIS volume, excellent in its production and a credit to the publishers, places upon the medical profession a real debt to its author and to the individual, past, and present members of the staff of the Pathological Laboratory of the Philadelphia Zoölogical Gardens whose work has made it possible. It is primarily a work in comparative pathological anatomy dealing with a zoölogical field which hitherto has been presented only in scattered journal articles and occasional sections of the annual reports of our larger zoölogical collections; and for this reason is virtually unique. It is based on the records of nearly six thousand autopsies performed during the past twenty years upon captive wild animals and birds which died in the Philadelphia Zoölogical Gardens. Pathology, as we know it, has been developed in connection with medical studies upon human beings, influenced of course by the contributions of modern veterinarians and those of experimental workers dealing with the small group of laboratory animals; and it is a welcome addition to have available for comparison such an analytical presentation of studies upon so large a zoölogical range, even if in the nature of all zoölogical collections, it is true that comparatively few individual specimens are included in the smaller subdivisions, *i. e.*, species and genera. That feature concerns little more than statistical questions of disease incidence, and in that scarcely more than prevalence in restricted groups, not matters of zoölogical range of any given affection.

In the nature of things to analyze adequately such a book is beyond the space reasonable for a journal review; it would almost amount to a volume itself. The writer prefers therefore to limit himself to an expression of appreciation and to a superficial and general description. The body of the work is preceded by a sym-

pathetic and very interesting and readable foreword from the pen of Dr. C. B. Penrose, President of the Zoölogical Society of Philadelphia, to whom in a large measure the establishment of the laboratory of the Gardens was due and who has for the whole period of its existence been more than merely interested in its studies, himself a trained medical man and an experienced zoölogist. In the later pages of the book are included, and have essential value, chapters by Dr. E. P. Corson-White upon the relations of diet to disease, and by Dr. F. D. Weidman in a general review of animal parasites as they have been encountered in the course of these autopsies. The bulk of the book is taken up by Dr. Fox's analytical presentation of the autopsy records, statistical, descriptive and comparative. Each system of organs or individual organs is presented, as in most treatises upon special pathology, with the particular diseases affecting it as found in the different groups in the order of accepted zoölogical classification. This arrangement in itself lends itself well to comparison, and is often elaborated by special tabulations especially upon disease incidence. As a rule each organ receives from the author some outline of its normal and comparative anatomy and physiology preceding the detailed autopsy findings. Naturally the bulk of the text is devoted to descriptive matter, although the author is careful to avoid too much duplication and shows care in selection according to the importance of the various affections discussed; but most current readers will find their greatest interest attracted to the comments and summaries which the author has widely included, in which he has concentrated his interpretations and comparisons in relation to disease in human beings. The writer would offer as an example the very telling comparison in cardiac pathology between the hearts of birds and those of mammals. Birds naturally have a far higher bulk and weight development of the heart than do animals, their heart-body proportions being often twice that seen in the average mammalian species. But when the heart of a bird is subjected to unusual stress, it has less reserve for compensatory hypertrophy and is more liable to fatal effects. The mammalian heart is far more likely to show evidence of attempted compensation, is more often hypertrophied; and at death to show more signs of having withstood in lifetime all sorts of insults and strains; is more often manifestly and markedly enlarged by hypertrophy, is frequently the seat of "myocarditis" and of muscular degeneration. The writer suspects that the prevalence of arteriosclerosis is greater than is indicated in the Garden records, but the data obtained are at least suggestive, the incidence being highest in the family of hawks and vultures and followed at some distance and nearly alike by the carnivorous animals, the ungulates and the anserines. All four families are characterized by their need for extreme body exertion, thus stressing the mechanical factor of high blood-pressure, and the hawks and carnivores

adding the influence of protein diet. There have been comparatively few aneurysms met in the collection, none of them of the type of the important eroding saccular aneurysms of man; the usual syphilitic factor in the latter being largely replaced in the lower animals by animal parasites inhabiting the interior of the vessels, and both the shape of the aneurysms and the character of the wall differing in consequence. Why is it that the nephritis of animals, quite common among lower mammals, as in the wild rodents, does not more commonly have the usual human accompaniment of arteriosclerosis? Why do these wild animals, in the Philadelphia Gardens living in an industrial city and having a trunk-line railway extending along the longest boundary of the Gardens, have so little pneumokoniosis and virtually never the marked grades found in man? Why is it that the common diffuse atrophic pulmonary emphysema of old human beings and many domestic animals, such as horses, is absent from this collection of wild animals, even though many of the specimens attain what represents senility for them? On the moot point of the influence of biliary entrance into the pancreatic duct in the etiology of pancreatitis, Dr. Fox is able to call attention to the rarity of pancreatitis in birds, which as a class have the biliary and pancreatic ducts well separated (and this rarity in the face of a high incidence of duodenitis); and to a comparative incidence of 14.9 in mammals with proximity or combination of biliary and pancreatic ducts to 13.6 in those with distinct separation of these ducts. This offers some evidence in favor of the belief that bile may at times enter the pancreatic duct and be provocative of pancreatic inflammation. Considerable space is given to an outline of special studies by Dr. E. A. Schumann upon diseases of the female generative organs, represented in the laboratory material and upon questions of comparative obstetrics, the mechanism of labor in the quadrupeds, as illustrated in the Gardens.

As above said it is entirely impracticable to even mention the details of information collected in this volume. The work is in no sense a text-book either upon animal medicine or upon pathological anatomy; it is a work of reference for most students of scientific medicine. One man will be attracted because of the medical aspects of its comparative anatomy; another will find the bacteriological references of the pneumonias encountered of special interest and another the comparative anatomy of the miliary tubercle, as characteristically developed in man, in the bovine, in the monkey, in the bird.

The development of normal comparative anatomy was basic to the establishment of the principles of Darwinism. The broadening of our knowledge of comparative pathology will be found essential for the fixation of any comparable principles of pathology. Books like Bland-Sutton's *Evolution and Disease* are rare and possible only to men familiar with the sort of material embodied in Fox's

book; and it is as a source book for such information that the present volume is to be regarded. We can whole-heartedly congratulate the author upon the work and can as certainly hope for the appearance of more works of its kind. S.

DIABETES AND ITS TREATMENT BY INSULIN AND DIET. By ORLANDO H. PETTY, M.D., Professor of Diseases of Metabolism in the Graduate School of Medicine, University of Pennsylvania. Pp. 111; 6 illustrations. Philadelphia: F. A. Davis Company, 1924.

DOCTOR PETTY is to be congratulated upon his book on Diabetes, presented as a handbook for the patient. It details in a clear, logical and straight-forward way the subject of diabetes and will be a most valuable adjunct to the physician and to the patient in the handling of the latter's disease. The advice is practical and while here and there are terms and expressions which may be a bit difficult for the lay mind to understand, nevertheless on a whole it is so complete and yet sufficiently elementary that the patient may be able to follow its precepts without very much difficulty. M.

DISEASES OF MIDDLE LIFE. Edited by FRANK A. CRAIG, M.D., Associate Director of the Clinical and Sociological Department of the Henry Phipps Institute of the University of Pennsylvania. Pp. 1871. Philadelphia: F. A. Davis Company, 1923.

THE editor of this monograph states in his preface that the system is compiled "with the object of presenting to the medical profession a series of monographs covering those diseases which are most common during middle life or which have a bearing upon the health, efficiency and well-being of the individual during that important period." He furthermore states that there has been no definite limitation placed upon the period of life which is included under the title of middle life. With this advice in mind the twenty-two collaborators have presented a series of monographs which adhere more or less strictly to the purposes of the volume. They have endeavored, and for the most part successfully, to discuss those disorders which have to do with that epoch in the life cycle in which degenerative diseases begin to manifest themselves. As would be expected in a book of this type considerable space is devoted to diseases of the arteries, kidneys and the heart which preëminently have their onset at least toward middle life. These sections are

most admirable. Doctor Pepper, Doctor Piersol and Doctor Talley are to be congratulated on their presentations. These sections occupy a goodly part of the first volume. The second volume does not apparently carry out as successfully the purposes of the book as does the first volume. Several of the sections are apparently not written with the object of dealing with disorders of middle life but might well be monographs of diseases appearing at any age.

Taken as a unit, the book can be heartily recommended as an exposition of those disorders which are likely to attack an individual when they reach middle life. M.

PRINCIPLES AND PRACTICE OF OBSTETRICS. By JOSEPH B. DE LEE, A.M., M.D. Professor of Obstetrics at the Northwestern Medical School. Fourth edition, thoroughly revised. Pp. 1123; 923 illustrations. Philadelphia and London: W. B. Saunders Company, 1924.

IN every branch of medicine there are two or three text-books which are so far in advance of the average as to be looked upon almost as classics. In this class De Lee's book may be placed without any hesitation. The present edition has been brought up to the minute and naturally such revision has again added slightly to the size of the volume. The author is a conservative teacher who realizes that most obstetric cases are handled by general practitioners and therefore he does not always recommend procedures which only the skilled obstetric specialist can execute. The excellent index is a worthy feature. B.

MEDICAL GYNECOLOGY. By S. WYLLIS BANDLER, M.D., Professor of Gynecology, New York Post-graduate Medical School and Hospital. Fourth Edition. Pp. 930; 157 illustrations. Philadelphia and London: W. B. Saunders Company, 1924.

THE present edition is the first revision in ten years and contains new chapters on urinary diseases, radium, roentgen-ray, constipation and syphilis. Too much space is devoted to endocrinology in view of the present uncertainty in this field and throughout the book there is undue repetition. Many of the subjects are unduly elaborated upon, and it is the belief of the reviewer that if the book were considerably condensed its value would be considerably increased. There is very little in the book which is not well covered by the better general text-books on gynecology. B.

DIE RAUCHENDE FRAU. By R. HOFSTÄTTER, Lecturer on Obstetrics and Gynecology in Vienna. Pp. 266. Vienna and Leipzig: Hölder, Pichler & Tempsky A. G., 1924.

THE author announces this book as a clinical, psychological and social study of the effect of tobacco on women who smoke. The various organs of the female body are considered separately and at length with regard to the injury which can be caused to them by smoking and the effect of tobacco on feminine morals is fully discussed. The author vehemently opposes the use of tobacco by women, especially young women. An extensive bibliography is appended. B.

THE TREATMENT OF THE COMMON DISORDERS OF DIGESTION. A HANDBOOK FOR PHYSICIANS AND STUDENTS. By JOHN L. KANTOR, PH.D., M.D., Chief in Gastrointestinal Diseases, Vanderbilt Clinic, Columbia University; Associate Gastroenterologist and Associate Roentgenologist, Montefiore Hospital for Chronic Diseases, New York City. Pp. 245; 64 illustrations. St. Louis: The C. V. Mosby Company, 1924.

THE reviewer cordially recommends this sane, well written handbook to all physicians interested in the subject. There are excellent chapters on General Principles and Methods, The Management of Functional Digestive Disorders, The Treatment of Ptosis and the Asthenic State, Treatment of the Syndrome of Gastric Irritation, of Gastric and Duodenal Ulcers, of Delayed Gastric Emptying, of Constipation, of Achylia Gastrica, of Gall-bladder Disease, of Diarrheas, and of Headaches Associated with Indigestion. The subject matter is presented clearly and simply and is excellently illustrated. F-H.

HANDBOOK OF MODERN TREATMENT AND MEDICAL FORMULARY. A CONDENSED AND COMPREHENSIVE MANUAL OF PRACTICAL FORMULAS AND GENERAL REMEDIAL MEASURES. Compiled by W. B. CAMPBELL, M.D., Formerly Resident Physician at the Methodist Episcopal Hospital of Philadelphia. Seventh revised and enlarged edition by JOHN C. ROMMEL, M.D. and C. E. HOFFMAN, PH.M. Pp. 693; No illustrations. Philadelphia: F. A. Davis Company, 1924.

SEVEN editions of this book would seem to bespeak some inherent worth, which doubtless lies in the many formulæ that are to be found in it. As a manual of modern medical treatment, however, the book is incomplete and even crude. The first recommendation for

"Appendicitis" is castor oil "to unload the bowels if operation is refused." Diabetes mellitus, according to the authors of this curious volume, "can affect one of normal development as well as can the diabetes produced by brain and pancreas disease." The treatment of meningitis contains no mention of antimeningococcic serum. Seven pages are devoted to syphilis, but not one word is to be found concerning salvarsan and its successors. F.-H.

A DICTIONARY OF TREATMENT INCLUDING MEDICAL AND SURGICAL THERAPEUTICS. By SIR WILLIAM WHITLA, M.D., D.Sc., LL.D., M.P., Emeritus Professor of Materia Medica and Therapeutics in Queen's University, Belfast. Seventh edition. Pp. 1100. New York: Paul B. Hoeber, Inc., 1924.

A MONOGRAPH upon the treatment of some twelve hundred different pathological conditions in the fields of medicine, surgery and the specialties could hardly be expected to be up to date in all particulars. However, in these pages the reader will find few omissions of importance. The arrangement and treatment of the subject matter is such as to render this a valuable therapeutic reference book for the general practitioner. A.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI,
CINCINNATI, OHIO.

Clinical Studies on Venous Pressure.—EYSTER and MIDDLETON (*Arch. Int. Med.*, 1924, 34, 228) consider that the taking of the venous pressure in the peripheral veins of a patient at bed rest gives valuable information of beginning cardiac decompensation. Venous pressure rises quite definitely before any other clinical signs of failure are evident. They strongly recommend keeping a close watch on it in cases of pneumonia and other forms of impending decompensation, and to be guided by it in deciding treatment, rather than to wait for other clinical signs. Venesection, while producing only a very transitory effect on the venous pressure in people with normally functioning hearts, cause a rapid fall in the pressure in cases of cardiac decompensation. This fall, too, may be maintained for prolonged periods in such cases, the heart increasing in efficiency as its engorgement is eliminated. Development of valvular lesions in acute rheumatic fever results in alterations of the venous pressure only when cardiac decompensation supervenes. So long as the heart is compensating the pressure remains normal. The anemias, even with the blood viscosity lowered to half, fail greatly to alter the venous pressure.

The Rational Use of Duodenal Drainage.—JONES (*Arch. Int. Med.*, 1924, 34, 60), in his survey of the results of duodenal analysis in 274 cases, brings out several interesting points regarding the practise of duodenal drainage. Its greatest value, he feels, is its high percentage of definite indications of the presence of gall stones, even when many of his cases were negative as regards history, physical examinations and roentgen-ray findings, the positive signs arrived at from duodenal analysis being confirmed at operation. His analysis consisted mainly

of microscopic examination of the sediment obtained by high speed centrifugation of the drainage samples. In the cases of gall stones characteristic elements were present in the sediment, these consisting of bile-stained epithelium and leukocytes, crystals of cholesterin, bilirubin and calcium bilirubin in abnormal amounts. Any or all of these may be found in either cholecystitis or cholelithiasis, but only in the later disease do the findings exhibit a considerable degree of constancy, especially the large amount of crystalline deposit. The author discounts greatly any deductions made as to the location in the biliary tract of the pathologic changes on the basis of the "A," "B" and "C" bile samples. Also, he criticises the belief that instillations of magnesium sulphate into the duodenum cause gall-bladder contractions and drainage.

Acute Pancreatitis.—EGGERS (*Ann. Surg.*, 1924, 80, 193), from a careful observation of 6 patients suffering from acute pancreatitis, concludes that the cause of the disease lies in the action of the bile when, and if, it is forced up into the duct of Wirsung. Disease of the gall-bladder was present in all 6 cases, with gall stones in 5 of them while 2 showed a definite jaundice at the time of the attack. Whether normal bile is capable of causing such trouble is questionable, but Eggers points out that the bile here was not normal, since in every case gall-bladder infection had been present. That infection itself is not responsible for the toxicity is proved by several negative cultures from the peritoneal fluid in these cases. Eggers believes, then, that abnormal bile, entering the duct of Wirsung, starts the process, and that the subsequent necrosis is most likely due to both bile and pancreatic ferments acting on the surrounding tissues. At one autopsy necrosis was found only around the duct of Wirsung throughout its whole length. The cardinal symptoms of the disease are: (1) Pain, severe, often colicky in character; (2) vomiting; and (3) collapse. Physical examination reveals exquisite tenderness over the pancreas, with little or no rigidity. A polymorphonuclear leukocytosis is usually present. Treatment of the condition is considered to be surgical.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,
NEW YORK.

The Therapeutic Use of Digitalis.—The report of the committee appointed by the Council on Pharmacy and Chemistry outlines the limitations of digitalis therapy, and the methods of obtaining digitalis effects. ROBINSON, WHITE, EGGLESTON and HATCHER (*Jour. Am. Med. Assn.*, 1924, 83, 504) emphasize the dangers of digitalis therapy in partial heart-block, and particularly the intravenous use of digitalis

as an emergency measure in cases of sudden heart failure when a careful study of the heart has been impossible. Such therapy may prove fatal. In auricular fibrillation digitalis therapy is clearly indicated, and though rapid digitalization may be indicated, oral rather than intravenous or intramuscular administration is the method of choice. Digitalis may slow the ventricular action in cases of auricular flutter, and tend to increase the efficiency of the heart. In some cases digitalis may cause a disappearance of extrasystoles, and in cases where digitalis has not been administered their presence is not a contraindication to its use. In cases of complete heart-block the effects of the digitalis bodies on the conducting mechanism of the heart may be disregarded, and their use is not contraindicated. However digitalis should be withheld in cases of temporary block when a return to the normal rate is anticipated. Cases of chronic myocarditis with signs of cardiac failure and normal rhythm will often be greatly improved by digitalis therapy but such cases are often unusually susceptible to the toxic effects of the drug, and oral administration only should be used. Less benefit should be expected from digitalis in cases of aortic insufficiency though valvular lesions do not alter the indications. Only in the exceptional cases where it is imperative that digitalis effects should be obtained in two hours or less is intravenous or intramuscular administration justified, for the body has no way of ridding itself of an overdose when given intravenously or intramuscularly and we do not know how much will be required in any case to produce the desired result. In cases where nausea or vomiting contraindicate oral administration the desired therapeutic effect may be obtained by rectal administration. The total average dose of fairly active standardized digitalis by mouth for inducing full therapeutic effects within thirty-six to forty-eight hours in an adult who has not received digitalis within ten days is about 1.5 gm. of the leaf or 15 cc of the tincture. This may be given in divided doses every four or six hours, or half of the total dose may be given and the remaining half in two divided doses after four to six-hour intervals. If there is doubt about recent medication smaller doses of from 0.1 to 0.3 gm. of the leaf, or from 1 to 3 cc of the tincture should be given three or four times a day. Ambulatory adult patients may be given 0.1 gm. of the leaf or 1 cc of the tincture three times a day by mouth. In an emergency one dose of 0.5 mg. of crystallized ouabain or amorphous strophanthin is enough for intravenous or intramuscular injection, digitalis being given by mouth in doses of 0.3 gm. of the leaf or 3 cc of the tincture every four hours until the desired effect is obtained.

Treatment of Bilharziasis by Antimony Tartrate.—LASBREY and COLEMAN (*Brit. Med. Jour.*, 1924, 1, 907) explain and summarize the results of their treatment of 4600 cases of bilharzial disease in the Old Cairo Hospital in Egypt by means of sodium antimony tartrate. Intravenous injections of sodium antimony tartrate are thought to be less toxic than the potassium salt. The initial dose is 1 grain increasing $\frac{1}{2}$ grain each injection up to $2\frac{1}{2}$ grains which is the maximum dose. Daily injections for six days are given, then every other day until twelve injections or a total of 27 grains has been given. The full course is given until only "dead" eggs are reported. This method is used for both urinary and rectal cases of bilharziasis, and in the average case

20 to 30 grains is sufficient to effect a cure. Surgical conditions caused by the disease such as papillomata or perineal urinary fistula can be satisfactorily operated on after a preliminary medical course. The mortality among patients taking the course is 4.9 per 1000.

Carbuncle and Its Treatment by Magnesium Sulphate.—MORISON (*Brit. Med. Jour.*, 1924, 1, 703) reports the successful treatment of 28 cases of carbuncle with a magnesium sulphate paste. The paste is composed of 1.5 pound of dried magnesium sulphate mixed with 11 ounces of glycerine acid carbolic or pure glycerine in a hot mortar and preserved in a covered jar. The paste is applied once or twice a day to the carbuncle, and after a few days the central slough separates leaving a raw granulating ulcer. This is dressed with the paste until healthy granulation tissue appears, then the cavity is packed daily with sterile gauze soaked in a solution of magnesium sulphate made by dissolving 40 ounces of magnesium sulphate in 30 ounces of boiling water and 10 ounces of glycerine and sterilizing in an autoclave. When the healthy granulation tissue is level with the surrounding skin it may be covered with Thiersch skin grafts or allowed to epithelialize. The advantages of this method are: (1) No surgical interference is required; (2) its application is simple and dressings infrequent, once or at most twice a day; (3) the combined osmotic action and its inhibitory effect on the growth and development of the staphylococcus cleanse the wound and assist in the separation of all sloughing and unhealthy tissue; (4) the granulations formed are firm and solid and lend themselves admirably as a base for a superimposed skin graft.

An Antidote for Arsenic, Bismuth, and Mercury Poisoning.—Substantiating the results reported by McBRIDE and DENNIE (*Arch. Derm. and Syph.*, 1923, 50, 63) SIMON (*Brit. Med. Jour.*, 1924, 1, 662) reports 8 cases of metallic poisoning treated by the intravenous administration of sodium thiosulphate and confirms the claims made for this method of treatment in cases of poisoning by arsenic, bismuth, and mercury. Mercury and bismuth stomatitis cases were quickly relieved by three to four intravenous injections of 0.45 to 0.6 gm. of sodium thiosulphate dissolved in 5 cc of water on alternate days.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

The Lange Gold Chlorid Reaction on the Cerebrospinal Fluid in Infants and Young Children.—GRULEE (*Am. Jour. Dis. Child.*, 1924, 28, 147) found that in congenital syphilis the colloidal-gold reaction in the spinal fluid may assume at times the same degree as that shown in cases of parietic dementia. In this series this occurred twice in cases

of syphilitic meningitis. Congenital syphilis varies rather frequently from the usual reaction that is a fluid which shows the greatest reaction in dilutions of 1 to 40 and 1 to 80. There is no regular agreement between the blood Wassermann and the Wassermann and colloidal-gold reactions in the spinal fluid. There may be a strong reaction both to the Wassermann and to the colloidal-gold solution in the spinal fluid with a negative blood Wassermann. Tuberculous meningitis more nearly conforms to the reaction with greatest intensity in dilutions of 1 to 160 and 1 to 320. It may vary considerably from this in certain cases showing a progressive variation as the meningitis extends. Other conditions which clinically may be easily confused with tuberculous meningitis may show a colloidal-gold reaction not dissimilar from that which is seen in certain cases of tuberculous meningitis. There is no definite reaction in most cases of idiocy and epilepsy.

The Prognosis of Sequelæ of Epidemic Encephalitis in Children.
KENNEDY (*Am. Jour. Dis. Child.*, 1924, 28, 158) studied 61 cases of residual epidemic encephalitis in children under fourteen years of age. Fifty-two of the patients were traced from the time of their first visit until the time of the report; 21, 16 of whom were traced, presented the Parkinsonian syndrome; none were improved; the condition of 2 was stationary and was worse in 14; 1 died from an intercurrent infection. The prognosis in this condition is not bad as regards life, but is poor as regards improvement or recovery. Twenty-three had changes in behavior and personality; 6 were improved, and 17 showed no improvement or had become worse. The lack of restraint exhibited by these children does not necessarily imply any great degree of mental impairment. Nineteen presented disturbances of sleep; 9 of these are now sleeping practically normally; 3 still show more or less disturbance and 7 are the same or worse. The respiratory syndrome occurred in this series much more commonly than is indicated in the literature. Two of the 17 children who had this sequela are well, 3 are improving and the condition of 12 remains unchanged. In a group of 6 children who suffered from the acute illness before the age of four years the after-effects were deplorably severe. One child is well; 5 of the children are mentally deficient as a result of encephalitis; of these 1 is deaf, dumb and blind; 2 are high-grade idiots; 1 suffers from a right hemiplegia, deaf mutism and generalized convulsions of the grand mal type; the other is mentally deficient and has grand mal attacks. In this series the frequency of the disease among the children of lesser years has been fortunately low, as the prognosis in these children is uniformly bad.

The Effect of Pregnancy on the Course of Scurvy in Guinea-pigs.—GERSTENBERGER, CHAMPION and SMITH (*Am. Jour. Dis. Child.*, 1924, 28, 173) observed that pregnancy modifies both the clinical and pathological picture of scurvy in guinea-pigs. The symptoms accepted at present to be characteristic of advanced scurvy are entirely absent or appear much later, and are much less severe than in non-pregnant guinea-pigs. The daily intake of 5 cc of fresh orange juice supplies the pregnant guinea-pigs, of an average weight of 500 gm., at least as much antiscorbutic material as these animals will consume of their own accord when free to feed on greens. The life term of the pregnant

scorbutic guinea-pig on a proscorbutic diet is on the average the same as that of the controls, even though the clinical and pathological picture of scurvy is mild in the former and severe in the latter. It is suggested that probably the change in the picture of scurvy in the pregnant guinea-pigs is due to the changed metabolic conditions produced by pregnancy, which either raise the resistance of the animal to infections or enable it to economize in the use of antiscorbutic vitamin. It is suggested that even though symptoms of scurvy in the pregnant guinea-pig are milder in degree, the animal's death after parturition is, nevertheless, due to the inadequate intake of the antiscorbutic vitamin.

The Food Requirements of Malnourished Infants with a Note on the Use of Insulin.—MARRIOTT (*Jour. Am. Med. Assn.*, 1924, 83, 600) points out that some infants fail to gain even when the nutritional requirements have all been met. In these infants it is necessary to resort to means for increasing the capacity of the infant for utilizing food. The most effective means in his experience has been transfusion. He gives such infants repeated transfusions of matched citrated blood. The amount given at a transfusion is about 1 ounce of blood for each 3 pounds of body weight. Very often an infant will begin to gain following transfusion, although the feeding is not changed. Besides oral methods of administering foods, the intravenous method may be used. Glucose can be given intravenously in a 20 per cent solution provided the injection is given slowly. The amount of the injection should be from $\frac{1}{3}$ to $\frac{1}{2}$ ounce of 20 per cent solution per pound of body weight. Glucose given in this way is only partly utilized, but if insulin is given at the same time better utilization of the sugar occurs, and a gain in weight of the infant is the result. Insulin is used in those cases because of the observation that diabetic patients on insulin treatment often gain in weight at a phenomenal rate, even when the food intake is not excessive. There would seem to be a good explanation for this observed fact. Marriott found that the best results were obtained when considerable amounts were given. He recommends the use of a 20 per cent solution of glucose containing 15 units of insulin per 100 cc. Such a solution has sufficient glucose to completely act as a buffer to the insulin. No bad results were observed. The injections may be given daily over an extended period. He found the results uniformly successful. A gain in weight nearly always occurs, even in cases where infection is present. The weight gained is not subsequently lost when the injections are finally discontinued. Marriott has not used this procedure routinely but has confined its use to the most extreme cases of athrepsia.

Intestinal Obstruction in Children.—LADD and CUTLER (*Boston Med. and Surg. Jour.*, 1924, 191, 141) analyzed 88 cases of intussusception and 17 cases of obstruction from other causes. The youngest patient was three weeks old and the oldest was almost nine years of age; 66 patients were under one year of age; 2 cases of intussusception occurred as a sequel of appendectomy (1 of these occurred before the patient was discharged from the hospital, and the other two or three days after his discharge); 1 case occurred during an attack of diarrhea and 1 case followed purpura. In patients in whom the invaginated

bowel had not become so swollen and edematous that it could not be reduced the mortality was high but not excessive. In this series there were 72 such patients operated on; 14 patients died and 58 recovered, a mortality of 19.4 per cent. Among the remaining patients on whom resection or enterostomy was performed the mortality was very high. Of 9 cases in which resection and lateral anastomosis was performed 8 died. The 17 cases in which obstruction was due to other causes than intussusception there were 3 which were subsequent to operation for intussusception; 2 cases were the result of Meckel's diverticulum becoming adherent across the ileum; 1 child died and 1 recovered; 3 children had obstruction during the first ten days of convalescence following operation for appendicitis with peritonitis; 3 cases, developed months after appendectomies with drainage, recovered by freeing the bands of adhesions; in 1 patient, from whom an enormous mesenteric cyst had been removed, obstruction resulted from a combination of narrowing the lumen of the bowel and adhesion of the appendix to the site of excision; there was 1 case of strangulation of a loop of ileum through a defect in the mesentery. In these 17 cases of obstruction from varied causes enterostomy was performed 6 times with successful outcomes in 5 instances.

Intracranial Hemorrhage in the Newborn.—SHARPE and MACLAIRE (*Am. Jour. Obst. and Gynec.*, 1924, 8, 172) found that in 100 consecutive deliveries that 10 per cent of the babies showed in the spinal fluid evidences of intracranial trauma. In 4 cases the cerebrospinal fluid was bloody, and in 6 cases it was yellow, in only 4 of which it was possible to demonstrate red blood cells. The yellow spinal fluid of newborn infants is probably the result of transudation of the blood plasma when red blood corpuscles are absent, and due to minute hemorrhages when red blood corpuscles are present. Of 4 cases of icterus neonatorum in this series only 1 had yellow spinal fluid. Early lumbar puncture is advocated in the absence of shock, not only for its diagnostic value, but also for its therapeutic value in early cases of cerebral hemorrhage and cerebral edema. Repeated spinal drainage at least every twelve or twenty-four hours is indicated, dependent on the size of the extravasation or the amount of cerebral edema as indicated on the spinal manometer. A modified subtemporal decompression and cranial drainage should be advocated only when the lumbar puncture drainage fails.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY AT THE SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA.

Dermatoses Due to Cosmetics.—COLE (*Jour. Am. Med. Assn.*, 1924, 82, 1909) discusses in a brief summary the enormous increase in the use of cosmetics, and the dermatoses definitely attributable to

them. He classifies the reactions produced under the head of the poisonous drugs contained in the preparations. Dermatitis from hair dyes containing as high as 23 per cent lead acetate and lead carbonate or "flake white" used in face enamels to give them a soft feel, and cases of lead line, lead palsy and gastrointestinal disturbances due to lead carbonate or flake white, are among the most important and serious intoxications. Mercurials are responsible for pigmentation, as in the pigmentation reported by Goeckerman as due to calomel in face creams, and for dermatitis from mercuric chlorid in bleaches, in which the drug is found sometimes in a concentration of 1 to 200. Most so-called "rice powders" contain no rice, and do contain large amounts of bismuth, responsible for occasional poisonings. Severe dermatitis with swelling of the eyelids is reported from the use of a hair tonic containing 1.06 grains of arsenious acid to the fluidounce. Wood alcohol was shown by Newcomb to be present in 20 of 66 toilet preparations examined. Mild and occasionally severe dermatitis is produced by depilatories. Paraphenylenediamin is one of the most grossly abused and common of the dermatitis-producing drugs. It is a common ingredient in hair and fur dyes, and produces a remarkably severe and intractable dermatitis. From February 13 to September 4, 1909, 32 cases were reported to the American Medical Association alone. France Germany and Austria have prohibited the use of this drug entirely. Oxidation with hydrogen peroxid stops the action of the dye, but does not necessarily protect against the dermatitis. It has recently been marketed as an ingredient of eyebrow paints. The author has also seen examples of dermatitis of the face and neck traceable to the preparations now in use for sleeking down the hair.

Bilirubinemia in Patients Treated with Arsphenamin.—SCHAMBERG and BROWN (*Jour. Am. Med. Assn.*, 1924, 82, 1911) report a series of studies of the bilirubin content of the blood in patients under treatment with arsphenamin. They find in confirmation of the findings of Chargin and Orgel, and of Greenbaum, that a bilirubinemia may follow the administration of the arsphenamin, but that it has no relation to the number of injections of the drug administered, and is apparently a matter of individual idiosyncrasy. They believe the van den Bergh method to be of practical value in determining the latent jaundice of patients under treatment, and note that it is preferable to examinations for bilirubenuria. MacCormack and Dodds (*British Med. Jour.*, 1923, 1, 1200) found that liver reserve is so great that the ordinary course of 8.7 gm. of neoarsphenamin has no significant damaging effects.

Hexamethylene Dermatitis in the Rubber Industry.—CRONIN (*Jour. Am. Med. Assn.*, 1924, 83, 251) reports an occupational dermatitis affecting 60 workers in a rubber factory, which was traced to hexamethylene which is used as a catalyzer in the vulcanization of rubber. The amount of the drug did not exceed 1 or 2 ounces in 100 pounds of rubber stock, yet severe and intractable cases were traced to the heel room where rubber heels were removed from the hot vulcanizing presses, and continued to appear for many weeks sporadically as the scrap rubber containing the drug was used up, even after the main supply had been cut off. As is usual in epidemic occupational derma-

toses, an infectious factor made itself manifest in the form of furuncles and abscesses in the affected workers. Local applications were not successful in controlling the situation. The itching of the dermatitis of arms and face was a conspicuous symptom.

Chlorid Retention in Pemphigus.—KARTAMISCHEW (*Arch. f. Dermat. u. Syph.*, 1924, 146, 235) maintains that chlorid retention with marked reduction of sodium chlorid in the urine, when associated with eosinophilia, is a valuable aid in the diagnosis of malignant pemphigus, especially at the stage when only mouth lesions are present. The electrical resistance of the skin in this disease is normal.

Action of Silver Arsphenamin.—The following table which appears in a review in the *British Journal of Dermatology* (1924, p. 130) of an article by SATKE (*Dermat. Ztschr.*, 1923, p. 349) deserves reproduction in view of the scarcity of tangible data on the actual comparative efficiency of the arsphenamins which are on the market today. The author is quoted as considering silver arsphenamin as an effective drug for the removal of clinical signs of syphilis but as inferior to original arsphenamin and mercury treatment in permanence of results. He observed 2 cases of argyria after total doses of 15 and 16 gm.

Silver Arsphenamin.

	No. cases.	Cases followed.	Clinical relapse.	Serum relapse.	C. S. F. relapse.	Resistant W.R.	Dermatitis.
Abortive cases							
start	15	8	4	1			
Preventive cases	15	5	2	..	1	3	1
Secondary cases	53	22	11	5	5	11	3
Latent cases	17	4	..	4	..	2	2
Lues malignat	1	1	..	1			

Arsphenamin-mercury.

Abortive cases							
start	15	8	..	1			
Preventive cases	15	5	..	2			
Secondary cases	53	22	2	4	2	6	1
Latent cases	18	4					
Lues malignat	1	1					

The patients were all young women between the ages of fifteen and thirty years, and the two series were as nearly comparable as is reasonably possible.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

Natural Immunization in the Newborn.—MUSSELMAN (*Am. Jour. Obst.*, July, 1924) gives the results of his observations on this subject in the Department of Obstetrics in the Yale School of Medicine. He

found that with one exception only, in all his experience, the maternal serum had a higher value in producing immunity than the serum of the newborn. In some cases the serum of the infant failed to show any appreciable quantity of immunizing bodies; others have found that the newborn is independent of the mother for its antibodies. In examining infants prematurely born of mothers suffering from typhoid fever agglutinins were absent. Child born during the typhoid infection of the mother had a lesser immunizing value than those born of mothers who had typhoid fever just before pregnancy. When animals were immunized against typhoid and cholera during pregnancy, they gave birth to young having less agglutinin than the mother. Children born of tuberculous women usually showed some antibody in the blood stream. The content of bacteriolysins is higher in maternal serum than that of the newborn. The serum of the human mother possess a higher content of hemolysin than the serum of the child, which in many cases fails to show any appreciable quantity. So far as opsonins are concerned, the maternal and fetal serum seems of equal value, both diminish during the first days of life and increase spontaneously; in precipitins the maternal serum was always higher than that of the child. The anti-ferment action of the mother's blood is greater than that of the newborn. It is difficult to harmonize all the findings reported by various investigators, it may be that placental transmission of antibodies depends upon the type of placentation, but it is interesting to note that from our clinical experience we find that if the mother has developed an infection such as typhoid fever or smallpox in the latter months of pregnancy, the child is more likely to show infection than if the disease had occurred in the early months of gestation.

Syphilis as a Complication of Pregnancy in the Negro.—BARTHOLOMEW (*Jour. Am. Med. Assn.*, July 19, 1924) analyzes his results in the study of 300 cases of syphilis in negro women. He describes 5 cases in which the symptoms varied so greatly that a diagnosis was difficult. He is accustomed to study his cases by a roentgen-ray examination of the fetal bones, microscopic examination of the placenta and a dark-field examination of material aspirated from the fetal liver. By this latter method he frequently detects spirochetes. In comparing the pregnancies of 100 non-syphilitic and 100 syphilitic patients without treatment and 100 syphilitic patients who received treatment, in a clinic where at least one-third of the patients are syphilitic, the syphilitic patients showed three times as many abortions and premature labors and seventeen times as many stillbirths as did those who were not syphilitic. Among those patients receiving treatment before labor, the number of premature births was reduced one-half; there were one-third as many stillbirths; one-seventh as many abortions and one-ninth as many infant deaths up to ten days as in those patients who received no treatment. The treatment employed was the giving of 1.14 gm. of arsphenamin and 0.04 gm. of mercuric salicylate, from seven months on to term. He believes that a dark-field examination on a suspension of liver tissue obtained at autopsy or aspirated from the liver is a valuable aid in diagnosing syphilis in the infant. Its results agreed with the maternal Wassermann reaction in 70 per cent of the cases.

The Care of Patients in Private Practice and the Physician's Responsibility.—At a recent meeting of the British Medical Association (*Brit. Med. Jour.*, August 16, 1924) in discussing the value of antenatal care, MacKenzie stated that a physician is not justified in accepting service for a confinement if the size of his practice, his other occupations or the state of health are to be made an excuse for his failure to carry out those measures of antenatal care, attendance during the actual confinement and postnatal watchfulness which are in accordance with modern knowledge and hospital practice. He considers the responsibility of maternity practice greater than any other assumed by a physician. His practice has averaged 3700 visits and 2400 consultations yearly with 11,200 miles of traveling. The average number of confinements yearly has been 77, a third of whom were primiparæ. His patients are the families of fishermen, farm laborers and cottagers. In very few houses are there conveniences of any kind and water is brought from outside wells or pumps. Under these conditions he has tried to carry out antenatal care and modern practice. When engaged for a confinement he visits his patient, makes an examination thoroughly and instructs the patient carefully about the hygiene of pregnancy. He leaves with her a printed pamphlet and insists that samples of urine be sent regularly. He again sees his patient about the fifth month, confirming his estimate of the period of pregnancy, measuring the pelvis and repeating his general examination. He explains the preparation for confinement and inspects the bed which the patient proposes to use. His last visit before confinement is a week before the expected time. Examination is repeated and especially to ascertain the presence or absence of descent and engagement. The success of this method has been to physician and patient most gratifying. In 680 confinements of which 224 were primiparæ, there has been no maternal death or infection and 11 stillborn children. Of these 3 were monsters; 2 had spinæ bifida; there were 3 cases of eclampsia and 4 cases of antenatal albuminuria. Labor was premature in 13 and the placenta had to be removed manually in 14. The forceps was used in 212 cases and in 151 the perineum was repaired. Eighteen breech presentations and 4 shoulder presentation were included. His preparation for actual confinement is thorough cleanliness, the emptying of the patient's bowels and bladder and an efficient nurse in attendance. Lysol, a pound package of cotton and two deep basins are provided. The bed is supported by boards slipped under the mattress which is covered with thick brown paper or water-proof sheeting. When labor starts a dose of castor oil is taken followed by a copious enema. With these simple methods his practice has been satisfactory to his patients and to himself.

Maternity Work Among Soldiers' Wives.—Moss (*Brit. Med. Jour.*, August 16, 1924) reports his results in attending confinements among soldiers' wives in the hospital at Aldershot. There were 1850 cases and only 4 who had not attended the antenatal clinic. Among those who had received antenatal care, there was 1 death from pulmonary embolus on the seventh day which followed septic infection in a case of perineal laceration and forceps delivery. If officers' wives are included; there were over 2000 confinements with 1 death among those who received antenatal care. There were 2 deaths of patients admitted

in a dying condition, 1 from advanced disease of the heart, the other from antepartum bleeding. There was no difficulty in conducting antepartum examinations or care, as patients welcomed such attention. Among the cases were 8 Cesarean sections, 2 for placenta previa, 1 for tumor in the cervix and 1 for fibroid in the uterine wall. The others were for contracted pelvis. Three cases of eclampsia with fits recovered. Several women had threatening symptoms, but did well with care. The forceps was used in about 7 per cent of the cases. The writer is especially impressed with the value of external version. This he performed in 54 cases of breech presentation without using anesthesia. He recognizes the fact that this manipulation may cause accidental hemorrhage by a separation of the placenta. In 3 cases the fetal legs were extended and version failed. One case where the fetus weighed 24 pounds, was mistaken for twins. The child was delivered stillborn and the mother had some laceration. In the last four years there were no cases of sepsis. Before that there were 3 cases where the blood was sterile, but the discharge from the genital tract contained bacteria. These recovered after treatment by swabbing out the uterine cavity with 1 to 500 acriflavine solution. The writer lays stress upon examining the outlet of the pelvis in all patients pregnant for the first time. His antenatal equipment consists of a pelvimeter, stethoscope, urine-testing outfit, blood-pressure outfit and rubber gloves. In discussion upon the general subject of antenatal care, Adamson, of Leeds, spoke of experience in 4958 patients in private practice and among those working in factories during the recent war. Among the factory workers, there were 40 confinements with an average of 39 living children. Some of these women had difficult and unsuccessful labors previously. It was customary in these cases to examine the vaginal secretion and also to make a Wassermann test of the blood. Among the hospital population of Leeds rickets is not uncommon. Cesarean section is often necessary. The toxemia of pregnancy is very common and many cases are brought in neglected and in serious condition. Placenta previa is common and these cases frequently are neglected in the early stages. The type of syphilis seen among these patients was mild. Bourne urged that hemorrhage before labor in late pregnancy where the presenting part is not engaged should be regarded as placenta previa and pregnancy ended as soon as possible. Where the head was engaged, if the patient had albuminuria or edema, the treatment should be rest, dieting and sedatives. Johnstone of Edinburgh recalled Ballantyne's work in this connection. To illustrate its success, he reported 58 cases of albuminuria admitted for treatment of whom only one developed eclamptic fits. He thought pelvimetry valuable and employed vaginal examinations to measure the outer conjugate. To bring on labor he used quinin, castor oil and pituitrin. If this method failed, he used bougies. Others drew attention to the fact that vaginal examinations can be safely omitted in most cases and that regulation of diet can be employed where in previous pregnancies the child has been overdeveloped. The value of antenatal clinics and staffs was illustrated by the reports of five hundred and fifty of these clinics. The trend of the papers and discussions was to emphasize the value of antenatal care in connection with hospital confinements. Antenatal clinics should be in charge of obstetric specialists and those who have had considerable experience.

The Value of Blood Chemistry in Pregnancy.—From the laboratories of the Naval Medical School at Washington, BUNKER and MENDELL (*Jour. Am. Med. Assn.*, September 13, 1924) report studies in the blood chemistry in pregnancy in 52 patients. Between the second and third months there were only six tests made, but for each of the succeeding months there were from nine to twenty. A chart is given of the monthly average of a normal fetal growth showing the various elements in excretion. A detailed table is also published giving the findings in normal cases. The writers have found variations in considerable quantity among many of the patients observed. In normal cases the curves of uric acid and cholesterol are almost parallel. This latter substance possesses antitoxic properties, so that its presence is a preventative, quite counter-balancing the toxicity produced by uric acid. From this a practical application suggests itself, that a diet rich in cholesterol during the latter part of pregnancy would be advisable, especially in cases showing a tendency to toxemia. Experiments made in the production of cholesterol by certain fats show that cream, butter, mushrooms, egg-yolks, alligator pears, oatmeal, salmon, black bass, olive oil, cod-liver oil and other fats increase the quantity of cholesterol. The last reading in these substances was in a patient at six months who subsequently had a long labor, developed sepsis and made a tedious and complicated recovery. The pathologic cases comprise 17, varying from mild toxemia to convulsions with coma. There were 5 cases of eclampsia in which the chemical examination of the blood gave findings within normal bounds. A follow-up report shows that these patients had no kidney improvement on their recovery. In 1 case admitted at term in convulsions, blood was obtained within less than one hour of a convulsion. Mother and child recovered and subsequently went through normal pregnancy and labor. In a subsequent pregnancy she was admitted again to hospital at eight months in convulsions with normal blood findings. The patient died. At autopsy the pathologist reported the liver changes typical, with acute terminal nephritis. In the nephritic toxemia blood chemistry showed nitrogenous retention of varying degree and in these cases a kidney lesion persisted to some extent. Nephritic cases with high blood-pressure showed retention of nitrogen with high uric-acid content. In the nephritic cases the cholesterol values are uniformly high. When the average findings in these cases are studied, it is interesting to observe how little difference there is between charts of normal cases and eclampsia, and what a wide difference there is between eclampsia and nephritic toxemia. Where eclampsia was pronounced the blood chemistry was practically normal. Where toxemia was the important feature without convulsions, there was decided nitrogen retention. On this finding the writers divide their cases of toxemia into eclamptic and nephritic toxemia. They realize that their number of cases is comparatively small, but they believe that the results are of wide interest. The reviewer would call attention to the fact that it has long been recognized that eclamptic convulsions are a conservative process and tend—if they are not in excess—toward the patient's recovery. Convulsions cause relaxation of the bloodvessels, often perspiration, a discharge of urine and feces and frequently bring about labor. The fact that patients sometimes recover after many convulsions and others die quickly who have none illustrates these facts.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, MEDICAL SCHOOL, UNIVERSITY
OF PENNSYLVANIA, PHILADELPHIA.

Surgical Treatment of Uterine Prolapse.—The operative treatment of uterine prolapse has always been far from standardized, and the results of any method of treatment have all too frequently been discouraging. Some men are most enthusiastic about a certain operation, perhaps their own invention, while others will almost swear by an operation based upon entirely different principles and yet both groups will have some good results and also some very poor ones if they take the trouble to follow their cases over a period of a few years. Under these circumstances there should be some value in obtaining the opinion and advice of a man who has had many years' training in gynecological surgery and has tried many of the numerous operations devised for the cure of this distressing condition. Such a man is MEYER (*Med. Jour. Australia*, 1924, 1, suppl. 177), who is consulting surgeon to the Women's Hospital in Melbourne. If the patient is in the child-bearing period the first object is to restore the uterus to its normal position, to maintain its natural freedom of motion, to repair all weakness and injury of the pelvic floor; in other words, to restore conditions for a favorable pregnancy and delivery. In the first degree of descent which has followed on childbirth there has been injury to the perineum, more or less stretching and tearing of the levator ani muscles, the rectovaginal and vesicovaginal fasciæ. Perineorrhaphy with strengthening of the anal sphincter and anterior colporrhaphy are essential in every case. Even with a very small cystocele it is wise to anticipate an increase and to correct it. In a considerable proportion of cases with a moderate degree of descent of the uterus colpoperineorrhaphy and anterior colporrhaphy will give the uterus back its natural support and preserve its fitness for childbirth. If there is a tendency to backward displacement the reconstruction of the pelvic floor will in most cases correct that tendency. When there is any doubt about the matter the author makes a small abdominal incision and plicates the round ligaments. He has given up the Alexander operation after a long experience with it. In the second degree of prolapse, after repair of the pelvic floor, if the round ligaments are firm and allow of a fair length of shortening, he performs anterior plication; one fold of each ligament is fastened to the anterior surface of the uterus and the two ends of the free loops are sutured together, thus combining a forward and a suspensory pull. His second choice in this type of case is the Gilliam operation. Its simplicity appeals to him, but he has never

quite satisfied himself that the pregnant uterus under the altered condition of the pull of the implanted round ligaments could be relied on to maintain the normal anteposition which makes for normal delivery, and he believes that occipitoposterior positions occur frequently after this operation. In cases of third degree prolapse (procentia), where the broad ligaments are nearly always relaxed from the long-existing drag, an excellent result is obtained by taking in the slack of each broad ligament and folding it posteriorly to the posterior surface of the uterus. The operation is very simple, the chief point to observe being the avoidance of the ovarian vessels, below which the sutures into the ligaments make their initial pass. Along with this a simple single surface to surface fold of the round ligament completes a measure which gives both elevation and direction to the uterus. After the menopause, unless some chronically enlarged or degenerate prolapsed uterus makes hysterectomy imperative, the author does a wide anterior and posterior colporrhaphy and perineorrhaphy supplementing it with either a Gilliam operation or a ventrofixation. In the event of a supravaginal hysterectomy the cervical stump is sutured to the ends of the broad ligaments.

High Voltage Roentgen Therapy of Cancer.—The new high voltage method of applying the roentgen-ray to cases of uterine cancer, which was introduced in Germany a few years ago was heralded as a very distinct advance in this field and was quickly followed by the roentgenologists in this country. Sufficient time has now elapsed since the introduction of this method for some definite statement as to whether it has proved to be all that it was heralded. It is of very great interest therefore to review an article by HERLY (*Jour. Radiol.*, 1924, 5, 71) based upon his personal observations and experiences during an extensive recent tour of most of the European medical centers and in which he quotes the views of many of the leaders in this field. He emphasizes that roentgen-rays do not directly kill the cancer cells, but they have a destructive action on all cells and when intensive radiation is given it will damage connective tissue, which must be regarded as a barrier to the cancer cell, and injury to it opens a breach in the protective wall, allowing an invasion of the cancer cells that are left unaffected by the rays. Since carcinomas are of different types and degrees of malignancy, not always distinguishable by the microscope, how can the same method of treatment and the same dose produce curative effects in all cases? Therefore a standard "carcinoma dose" of roentgen-rays cannot be established biologically. There is no unimpeachable proof that insufficient raying stimulates tumor growth. From the evidence at hand, the author states that there seems to be no reason why the old machines, as commonly used in this country for therapy, with increased distance, filtration and time, will not produce as good results as the high voltage apparatus introduced by the Germans. Intensive high voltage raying damages the normal tissues and damage to the endocrine glands reduces the general resistance of the patient and by itself even may lead to death. The condition of the organism in general cannot be neglected in seeking indications for roentgen-ray therapy, and it should be remembered that undernourished and cachectic individuals are roentgen-refractory.

Treatment of Chronic Gonorrhea in the Female.—Any logical method of treatment of chronic gonorrhea in the female necessitates the removal of the infection from the cervix, Bartholin's glands and Skene's glands. Since we are dealing with complicated glandular tissues, SHUTTER (*Wisconsin Med. Jour.*, 1924, 23, 69) believes that this can be best accomplished by their destruction with the cautery. In the case of the cervix this is usually done without anesthesia by the introduction of a small nasal cautery tip as far upward as the internal os. The current is connected and the tip drawn outward to the external os. If the vaginal mucosa is not touched by the heated instrument almost no pain is felt. One or two linear cauterizations are made and the operation is repeated several times at intervals of about two weeks. Erosions and Nabothian cysts respond readily to cautery applications. All patients are advised to keep the cervical secretions removed by the use of a daily douche. Moderate hemorrhage following cauterization is not infrequent and patients should be reassured against alarm. Novocain infiltration of the surrounding tissues is necessary before cautery destruction of the paraurethral glands, using a 2 per cent solution. The ducts are exposed with hair-pin probes and the fine cautery tip is then placed on the floor of the urethra and the ducts laid open throughout their entire length. While cautery destruction of the Bartholin glands and ducts is not difficult under local anesthesia, the area remains painful and tender for some time. Excision of the entire structure with the knife is simple, more effective and the postoperative course more satisfactory. The above routine has been more satisfactory to the author than any other measures previously employed. Chronic cases have yielded continued negative smears after from three to ten weeks. Where results have been poor careful reëxamination of the three possible foci has usually revealed the bacterial source. In several cases it has been impossible to obtain negative smears from the cervix because of the coexistence of chronic tubal infection. All patients are advised to remain quiet during the menstrual periods following cauterization, and because of the danger of extension of the disease treatment has seemed inadvisable for two or three days before and after menstruation.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

Deaths among Taxpayers and Non-taxpayers of Income Tax, Providence, 1865.—CHAPIN (*Am. Jour. Pub. Health*, 1924, 14, 647) states that in a city of over 50,000, in 1865, the death-rate in the families

of income taxpayers was less than one-half what it was among the non-taxpayers. This was not due to difference in age distribution nor to parent nativity. Though the figures for different causes are too small to warrant definite conclusions, or to permit further detailed study, they are certainly suggestive and warrant further investigation along these lines. However, one uncertainty common to such studies is minimized. An income tax seems to be a far better means of segregating persons of good economic status than do geographical distribution, number of servants or number of rooms in the house. When we have definitely determined the incidence of different causes of death on the two classes we will be prepared for what should be of great value, namely a study of the habits of life and of the environment which make for the longevity of the well-to-do.

Results in the Treatment of Congenital Syphilis.—FORDYCE and ROSEN (*Arch. Dermat. and Syph.*, 1924, 9, 355) have studied the results of prenatal treatment upon congenital syphilis. They have learned to be guarded in their opinion of the results of the Wassermann test on the blood from the umbilical cord. A long period of observation has shown that a positive Wassermann reaction at the time of delivery is not always evidence of syphilis in the infant, nor is the negative an indication that the child has escaped the infection. In the absence of clinical signs of the disease greater reliance should be placed on routine tests taken a week or ten days after birth, and thereafter every four weeks up to the age of six months. The interval may be lengthened to three months until the infant is two years of age, after which time an effort should be made to keep the child under observation for semiannual examinations for an indefinite period. If, at the end of two years the child has continued to have negative reactions in the blood and the spinal fluid, and is negative clinically, in all probability it is free from syphilis. The success of prenatal treatment depends on the duration of the infection, early administration of treatment and the amount tolerated. Microscopical examination of the placenta may prove of greater value in determining a latent infection than the result of the Wassermann reaction on the blood from the umbilical cord or from the veins during the early months of life. Occasionally cases of active syphilis with a negative serology are seen. Clinical manifestations must always take precedence over laboratory findings. The prognosis of congenital syphilis depends on the amount of prenatal treatment, the physical condition at birth, the severity of the infection, whether visceral, cutaneous or neural involvement is present, the time treatment is begun, the type of treatment and the toleration to treatment.

The Cause of Foot-and-mouth Disease.—A rare example of a reward for steadfast concentration on one problem by one man is to hand in the news that the virus of foot-and-mouth disease has at last been isolated by PROF. PAUL FROSCH, Professor of Dietetics and Bacteriology in the Konigliche Tierarztliche Hochschule in Berlin, working in conjunction with PROFESSOR DAHMER (*Lancet*, 1924, 206, 962). More than twenty years ago the author, working with Loeffler (*Jour. Comp.*

Pathol., 1899, 12, 79) discovered that a filtrable virus was responsible for foot-and-mouth disease. The author has worked at this subject with persistent diligence ever since, and at a meeting of the Berlin Microbiological Society, April 7, 1924, he was enabled to announce the discovery of a tiny bacillus which he has isolated and from which he has been able to reproduce the disease after thirteen subcultures. The organism is only 0.1 micron long in suitable solid medium, of the diameter of a red blood corpuscle, that is, 7 to 8 microns. This bacillus the two workers generously propose to name *Löffleria nevermanni*.

The Soluble Specific Substance of Pneumococcus—HEIDELBERGER and AVERY (*Jour. Exper. Med.*, 1924, 40, 301) have improved the method for the concentration and purification of the soluble specific substance of pneumococcus. Highly purified specific substance of Type II pneumococcus of polysaccharide nature was recovered essentially unchanged after precipitation by immune serum, by uranyl nitrate, by basic lead acetate or by safranine. Marked chemical differences exist between the specific substances of Type II and Type III pneumococcus, although both react as polysaccharides. The weight of evidence is considered to be in favor of the view that the specific substances of pneumococcus Types II and III are actually polysaccharide. The authors discuss the immunological significance of the foregoing view.

The Catalytic Action of Minute Amounts of Copper in the Destruction of Antiscorbutic Vitamin in Milk.—HESS and WEINSTOCK (*Jour. Am. Med. Assn.*, 1924, 82, 952) state that the antiscorbutic vitamin is readily destroyed by oxidation, especially when the oxidative process takes place in association with heat. This sensitiveness leads to a partial loss of this factor in the process of pasteurization. The gradual decrease of vitamin in the course of the "aging" of foodstuffs, such as vegetables, is to be interpreted in this way. Catalysis greatly increases the velocity of oxidation and thus furthers the destruction of this vitamin. A series of animal experiments demonstrated that when as little as 2.5 mg. of copper per liter, 2.5 parts per 1,000,000, were added to milk the antiscorbutic vitamin was appreciably reduced in the course of heating. Although copper does not go into solution to this extent in the course of well-supervised pasteurization, such contamination readily occurs when the equipment is not in good repair or well cared for. The risk is still greater in the process of condensing milk. A similar danger exists with regard to the contamination of butter and cream. The importance of copper in relation to these dairy products lies in the fact that we are largely dependent on them for our quota of the fat-soluble (vitamin A), and that this vitamin is also highly sensitive to the destructive action of oxidation. The circumstances may be the same in relation to other foodstuffs rich in one or both of these nutritional factors, for example, the green vegetables. At present contaminations of food with copper or other metals are judged by the standards of toxicology. This criterion is manifestly inadequate, for even non-toxic traces of these substances suffice to bring about the catalytic destruction of the vitamins.

Deaths and Disabilities from Heart Disease.—HEFFRON (*Am. Jour. Pub. Health*, 1924, 14, 652) states that heart disease causes more deaths and more disability than any other disease. Heart disease is due to an infection. Infections are more easily contracted by exposure when in a condition of undernourishment, or of fatigue, or when resistance is lowered by an unduly prolonged spell of cold or of hot weather. The danger of infection is greatest in children. Many of the infections which cause heart disease enter the blood stream from diseased tissues in the mouth and nose. All diseased tissues in the mouth can be removed without danger and without damage to the general health, and with marked improvement and increased safety. All infections should be avoided by avoiding contact with the sick or by active immunization. Heart disease does not always show itself by symptoms which call attention to the heart. Attention to the details of personal hygiene is a protection against heart disease. No person knows whether he is sound or not without frequent health examinations.

Recent Investigations of Absorption and Excretion of Lead in the Organism.—AUB, MINOT, FAIRHALL and REZNIKOFF (*Jour. Am. Med. Assn.*, 1924, 83, 588) say that lead is absorbed more rapidly through the whole respiratory tract than through the gastrointestinal tract. It is carried in the blood stream as a phosphate. Lead is stored in the calcareous portion of the bones. Damage results only when lead is being transported after absorption or following release from the bones. In active plumbism lead is distributed more widely through the body than in the chronic inactive form of the intoxication. The administration of acids or alkalis, particularly when associated with a low calcium intake, accelerates the release of lead and its excretion. A positive calcium balance in the body favors retention of lead in the bones.

Persistence of Inspired Bacteria in the Lungs of Alcoholized Mice.—STILLMAN (*Jour. Exper. Med.*, 1924, 40, 353) states that when mice are exposed to an atmosphere containing certain bacteria in the form of a fine mist, the bacteria may be recovered from the deeper respiratory passages. Pneumococci which have reached the lungs of normal mice as a result of this procedure usually disappear within a few hours and give rise to no generalized infection. In mice intoxicated with alcohol, on the other hand, pneumococci persist in the lungs for a longer period and fatal septicemia frequently follows. Hemolytic streptococci and *Bacillus influenzae* generally persist in the lungs for about twenty-four hours. In intoxicated mice these organisms do not disappear so rapidly from the lungs and generalized infection is much more frequent. The experiments yield no evidence as to how alcoholic intoxication renders the lungs more permeable to inspired bacteria.

Typhoid Fever and Ice.—Owing to the fact that ice purifies itself in the process of freezing, typhoid fever has rarely been traced to the ice supply. In fact, very few instances are on record in which ice has been accused, and in these instances the evidence is far from satisfactory. Special interest therefore attaches itself to the report of an outbreak of typhoid fever due to infected ice. The outbreak, which

occurred in Elmira, N. Y., during the summer of 1923, included 37 cases. CONWAY (*Am. Jour. Pub. Health*, 1924, 16, 574) believes that in view of the facts presented there seems little doubt that the outbreak of typhoid was directly due to the consumption of the superficial layer of natural ice, harvested from the heavily polluted Chemung River, even though stored, as it was, for a period of from five to six or possibly seven months. He also warns against the use of iced drinks chilled with ice harvested from polluted sources, even though subject to several months' storage.

Effect of Fatty Acids on the Resistance of Mice to Transplanted Cancer.—NAKAHARA (*Jour. Exper. Med.*, 1924, 40, 363) declares that sodium oleate, oleic acid, linolic acid and linolenic acid injected into mice in suitable amounts induce a material increase in the resistance against subsequent transplantation of cancer grafts, although they fail to exert so marked an influence on cancer grafts already in place. Sodium palmitate and sodium stearate, on the other hand, do not produce immunity, at least in the amounts employed in the present study.

Immunity in Rocky Mountain Spotted Fever.—CONNOR (*Jour. Immunol.*, 1924, 9, 269) contrasts the behavior of the virus in the tick and in laboratory animals. He states that the fact that there are so few organisms in the blood may be the reason why the virus in this situation is not amenable to attenuation. In tick tissues and in the tissues of guinea-pigs the virus may be attenuated by drying in the cold, and after keeping for from five to thirty days at a below zero temperature the tissue is no longer virulent, but will produce immunity. The most effective method of using combinations of virus and immune serum seems to be where virus is given in rather large dose and allowed to grow for twenty-four hours when a dose of serum is given to stop the infection. Another method which is successful under limited conditions is the giving of large doses of mixtures of virus and serum. An immunity may be achieved which equals that following an attack of the disease. The same mixtures heated to 60° for twenty minutes have been ineffective. The virus-serum mixtures are applicable for the present to guinea-pigs only. It is questionable whether the same amount of immune serum which will protect a guinea-pig will do the same for a larger animal. A virus that is much more concentrated is desirable, and one that may be calculated as to its minimum infectious dose prior to administration. The fact that immunity depends only on the amount of virus given is brought out, the immune body having nothing to do with the production of immunity in another animal.

Notice to Contributors.—All communications intended for insertion in the Original Department of this JOURNAL are received only *with the distinct understanding that they are contributed exclusively to this JOURNAL*.

Contributions from abroad written in a foreign language, if on examination they are found desirable for this JOURNAL, will be translated at its expense.

A limited number of reprints in pamphlet form, if desired, will be furnished to authors, *providing the request for them be written on the manuscript*.

All communications should be addressed to—

DR. JOHN H. MUSSER, JR., 262 S. 21st Street, Philadelphia, Pa., U. S. A.

THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

DECEMBER, 1924

ORIGINAL ARTICLES.

PROGNOSIS IN ORGANIC HEART DISEASE.*

BY GEORGE W. NORRIS, B.A., M.D.,

PROFESSOR OF CLINICAL MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; CHIEF OF
MEDICAL SERVICE AT THE PENNSYLVANIA HOSPITAL.

Prognosis. In venturing a prognosis our view must be taken with a large background of perspective and not from a narrow field focussed upon the heart alone. More or less prolonged observation is usually necessary. A single examination, no matter how searching and complete, is apt to lend too much support to David's despairing dictum that "all men are liars." Our bodement must also include a careful inquiry into symptomatology. An answer to the question "What can he do?"—without fatigue, pain, dyspnea, cough, cyanosis or edema—will shed the light of truth upon many a doubtful case. Recurrent attacks of decompensation, especially if unprovoked, are of bad augury, and opinion should be withheld if the patient is seen for the first time while decompensation obtains. The age of the patient also has a bearing. If the disease develops in early adult life, the outlook is more promising than if it appears earlier or later, because the strain of growth is over, the likelihood of renewed infection is lessened, disease of other organs has not yet begun and degenerative arterial changes are still in the future.

We should bear in mind that factors which bring about cardiac decompensation are the same factors which cause death. They are four in number, their relative importance being in the order named: (1) Infection; (2) arteriosclerosis; (3) change of rhythm; (4) toxemia.

* Read before the American Climatological and Clinical Association, May, 1924.
(Angina Pectoris and the Tachycardias were discussed by other speakers.)

Social surroundings play an important role. A change of occupation may greatly change our predictions. "In youth the family history, in adult life the habits, and in later years the circumstances, should be carefully scrutinized." (Cowan.) The patient's temperament is often a factor of great importance. Finally the response to treatment—the ease with which compensation is established by rest, underfeeding and digitalis gives us still further clues as to the degree of myocardial impairment.

Remember that the *effort syndrome* engrafted upon an organic lesion may produce symptoms which unless recognized and properly evaluated may render prognosis erroneously austere.



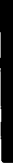


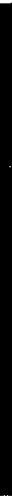
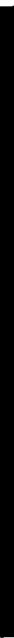






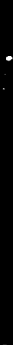

Prognosis will depend largely upon etiology. We no longer consider our cases as aortic insufficiency or mitral stenosis but rather as "mitral disease rheumatic with probably stenosis or aortic disease syphilitic, late," etc. In a similar manner we must properly classify the lesions primarily due to arteriosclerotic, renal or endocrine disturbances before venturing a prophecy.

Blood-pressure. In some cases of organic heart disease blood-pressure may have considerable prognostic significance. This applies chiefly to older individuals with myocardial rather than valvular lesions. Constantly high readings, especially of the diastolic pressure, indicate the degree of muscular strain to which the heart is constantly subjected and point strongly to renal lesions or other unknown toxic factors. This is generally recognized but it is worth while remembering that life insurance statistics indicate that 140/94 mm. represents the upper normal limit rather than 160/100 mm., which is generally accepted as the physician's standard. How greatly increased pressure above the expected normal influences the mortality rate will be seen in the accompanying table which shows, that an increase of from 25–34 mm. doubles and of + 50 mm. quadruples the death-rate. Abnormally low pressure on the other hand favors longevity, except in cases where it represents the terminal fall of an antecedent higher pressure. It has been estimated that including deaths from all causes the mortality of individuals with a pressure below 100 mm. was 65 per cent less than that expected.*

Sudden deaths occur in angina pectoris, in some aortic lesions and occasionally in mitral disease (from embolization or ventricular fibrillation). With these exceptions death from heart disease is usually a slow and torturing process. It is in my opinion also a fact that even in the absence of the first mentioned well-known causes, unexpected and unexplained arrest of heart action may result from purely reflex nerve influences. Sudden deaths, followed by careful autopsies with negative findings—we have all of us seen.

* Fisher, J. W.: Further Report of the Diagnostic Value of the Systolic and Diastolic Blood-pressure, Assn. Life Ins. Med. Directors, 1921,

SUMMARY OF THE MORTALITY EXPERIENCE OF THE NORTHWESTERN MUTUAL LIFE INSURANCE COMPANY, WITH RESPECT TO THE PALPATORY SYSTOLIC AND AUSCULTATORY DIASTOLIC BLOOD-PRESSURE.

Years of entry.	Range arterial tension.	Ages at entry.	Number of Lives.		Actual deaths.	Ratio actual to expected mortality (American men table).			
			Accepted.	Rejected.		100 per cent.*	200 per cent.	300 per cent.	400 per cent. Per cent.
1912-1920	Low blood-pressure 100 mm. and less	16-60	3389		26				**35.0
1915-1920	Diastolic blood-pressure 95 mm. and over	16-60	1244		22				78.6
1907-1910 to anniversary in 1919	Blood-pressure average 142 mm.	40 60	2610		310				94.0
	Blood-pressure average 153 mm.	40 60	520		90				114.4
High Systolic Blood-pressure by Ages.	Total	16-29		743	18				195.7
		30-39		731	34				259.5
		40-49		1196	181				334.6
		50-60		1495	274				190.8
		16-60		4165	507				230.5
Mm. over Average Systolic Blood-pressure for Age.	Total								136.1
		+10-14		525	26				183.8
		+15-24		1685	125				204.4
		+25-34		909	111				248.5
		+35-49		657	121				414.7
Total		16-60		4165	507				230.5

* The Northwestern Mutual Life Insurance Company's General Mortality Experience about 80 per cent of the Table. ** Estimated Mortality.

Risks REJECTED FOR HIGH BLOOD-PRESSURE ONLY.
 Years 1907-1920—Mortality Computed to Anniversary 1921
 Mm. over Average Systolic Blood-pressure for Age.

Rheumatic Endocarditis. Prognosis during an initial attack is good if, as is usually the case, the disease becomes arrested and if the original focus of infection can be found and eliminated. A much more difficult point to decide is, has the process become arrested? For this we must rely upon the absence of fever, increased pulse-rate, leukocytosis, anemia and precordial sensations. Needless to add, each recurrence of the infection increasingly favors a subsequent one, and each such attack tends to cripple the heart more and more. Again, the longer the infection remains clinically recognizable the worse the outlook. So too, the more valves demonstrably involved, the worse the prognosis.

In the quiescent stage, when presumably the patient has no longer an infection, but merely a mechanical handicap to withstand, prognosis depends upon the antecedent myocardial damage, the life the patient leads, and the type of valvular lesion. Other factors being equal, mitral stenosis¹ is worse than aortic insufficiency and the latter far worse than mitral regurgitation. It cannot, however, be too much emphasized that it is the infection of the myocardium that counts. To a good heart muscle the particular valve involved makes relatively little difference. "*Une maladie des valvules, ce n'est pas une maladie du coeur.*" What has been stated regarding the endocardium applies also to the pericardium. A pericardial effusion rarely causes death—it is the infection that kills. Pericardial adhesions may be a handicap, but it is the underlying fibroid myocarditis that brings the break in compensation.

In regard to acute and subacute (non-rheumatic) bacterial endocarditis, the prognosis is quite different. In the former condition death usually occurs within a month. In the subacute—frequently streptococcus viridans—type of infection the disease may masquerade as nephritis, pernicious anemia, meningitis or pneumonia, and so forth, and a correct diagnosis may be established only at autopsy. Intermissions—bacteria-free stages—are common and sometimes of long duration. Recoveries sometimes occur.

Syphilitic Cardiovascular Disease. In the first and second stages prognosis is good unless specific resistance to arsphenamin is present. This is even so in cases in which cardiac drugs alone have shown but little benefit. If, however, the combined treatment yields but little relief, the ultimate prognosis as to further improvement or cure is definitely bad (Brooks). Relapse after marked improve-

¹ Willus, F. A.: Life Expectancy with Mitral Stenosis: The cardiac mortality with mitral stenosis in Willus' series of cases was as follows: Complete series, 470 cases, cardiac mortality, 36.8 per cent after an average of 15.7 months. Mitral stenosis with auricular fibrillation, 116 cases, cardiac mortality 56.6 per cent after an average of 22.8 months. Mitral stenosis with presystolic or diastolic apical murmur, 253 cases, cardiac mortality 29.0 per cent after an average of 17.1 months. Mitral stenosis with presystolic or diastolic and apical systolic murmur, 197 cases, cardiac mortality 45.5 per cent after an average of 13.7 months. Significant T wave negativity, 50 cases, cardiac mortality 62.5 per cent after an average of 12.1 months. *Ann. Clin. Med.*, 1923, 1, 326.

ment is prognostically bad. Arrhythmia uncontrolled or with but little improvement has also an ominous augury. We must assume a permanent myocardial injury in all tertiary cases and advise accordingly.² In the tertiary stage arsphenamin and mercury are evanescent in effect. The danger of a Herxheimer reaction necessitates small doses and hence long treatment. Eradication of the spirochetes in their protected position is difficult. Nearly 70 per cent of Longcope's cases died within two years.³ Seventy-five per cent of all cases of aortic insufficiency in adults are syphilitic. Eighty per cent of these occur in men. Among untreated cases 30 per cent develop aneurysms. Thirty per cent have retracted valves and as a rule attention arresting symptoms appear about fifteen years after the initial infection.

Clinical Arrhythmia. *Premature contractions* (extrasystoles) have *per se* little prognostic significance. Occurring as they commonly do as a result of diverse reflex causes their seriousness is estimated by the basic heart condition. To this statement, there is, however, one notably exception. When they occur in combination with auricular fibrillation the mortality is almost as high as that of alternation.

Heart-block (auriculoventricular) when present to a degree which can be demonstrated without the electrocardiogram, is extremely serious. A few cases of the Adams-Stokes syndrome have been known to recover and live for years after severe and prolonged attacks. But there are many cases of non-convulsive block, which occur in lesser degree in association with rheumatic and other heart lesions, which, even while persistent, are compatible with prolonged though restricted life. The therapeutic block which digitalization produces in auricular fibrillation belongs to this group.

Alternation of the pulse is usually a forerunner of the end. Nearly 100 per cent of White's cases⁴ died within three years. I quite concur with Lewis⁵ who, classing it with subsultus tendinum and risus sardonicus describes it as "the faint cry of an anguished and fast failing muscle, which, when it comes, all should strain to hear, for it is not long repeated. A few months, a few years at most, and the end comes."

² Brooks and Carroll: Treatment of Heart Involvement in Syphilis, 300 Cases, Jour. Am. Med. Assn., 1914, 63, 1456.

³ Longcope: Factors in the Diagnosis and Treatment of Syphilitic Aortitis, Cleveland Med. Jour., 1914, 13, 141. Also Syphilitic Aortitis, Its Diagnosis and Treatment, Arch. Int. Med., 1913, 11, 15.

⁴ White, P.: Prognosis in Heart Disease AM. JOUR. MED. SCI., 1919, 157, 5.

⁵ Lewis, Sir T.: Clinical Disorders of the Heart Beat, New York, 1918, p. 111.

THE PROGNOSIS OF ANGINA PECTORIS.*

BY LOUIS HAMMAN, M.D.,

BALTIMORE, MD.

BEFORE I speak of the prognosis of angina pectoris it is necessary that I define clearly what I mean by angina pectoris. This is necessary because the term is used by physicians and medical authors in a different and almost contrary sense. Some employ it to designate a definite disease with peculiar clinical symptoms and characteristic anatomical lesions, while others employ it to designate a symptom that may occur in many different diseases and therefore without precise clinical or pathological implication. It is obvious that the prognosis of angina pectoris will vary widely with the definition adopted.

The name angina pectoris was introduced by Heberden. What he meant by the term is clearly stated in his classical description. "There is a disorder of the breast, marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it. The seat of it and sense of strangling and anxiety with which it is attended may make it not improperly be called angina pectoris. Those who are afflicted with it are seized while they are walking, and more particularly when they walk soon after eating, with a painful and most disagreeable sensation in the breast, which seems as if it would take their life away if it were to increase or to continue; the moment they stand still all this uneasiness vanishes. In all other respects the patients are at the beginning of this disorder perfectly well, and, in particular, have no shortness of breath, from which it is totally different."

By the contemporaries and immediate followers of Heberden, angina pectoris was used to denote the clinical picture he describes so well. It was only later that the clearness of the picture was blurred by the addition of spurious and irrelevant details. Conditions resembling angina, though but vaguely and remotely, came to be mistaken for it and finally distinctions were so far wiped out that almost every distress and oppression about the heart was called angina. To bring some order out of this confusion Forbes unhappily coined the term angina notha, spurious or false angina. This counterfeit angina was then subdivided into numerous groups, hysterical angina, toxic angina, vasomotor angina, and so on, until medical authors began to describe under the heading angina pectoris such a preplexing medley of symptoms that the original clear sense of the term was totally obscured. Confusion reached its high point in Germany fostered and encouraged by the great clinician Nothnagel. It was commonly stated that at least one-half the cases of angina were innocent functional disorders and that there was no

* Read before the American Climatological and Clinical Association, May, 1924.

sure way to tell the true from the false unless death arrived to give the distinctive stamp. In the latter part of the last century, Huchard fought valiantly to rescue angina pectoris from the perversions that had nearly robbed it of character and individuality. During the past twenty years, English authors, notably Mackenzie and Allbutt, have striven to revive the early definition of Heberden and to restrict the use of the term angina pectoris to the disease he so clearly and distinctly describes. With this reasonable and desirable endeavor I am entirely in sympathy and I shall use the term angina pectoris to denote a definite disease with a definite pathological anatomy.

It is scarcely necessary to plead justification for this choice. I am not here to describe the characteristic marks of the disease angina pectoris; I wish merely to state what every physician of experience knows, namely, that these marks are easily recognized. The diagnosis of angina pectoris is not more difficult than the diagnosis of any other clearly defined disease. Indeed I should say that for the most part it is less difficult. It is true that mistaken diagnoses are sometimes made and that occasionally the most experienced physician will waver in doubt. However, error and indecision are equally frequent in the diagnosis of tuberculosis, typhoid fever, cancer and every other well known disease. The perplexities of the diagnostic problem are no satisfactory excuse for vagueness in definition. If a disease is diagnosed typhoid fever and autopsy reveals it to have been miliary tuberculosis, we do not speak of miliary tuberculosis as pseudo or false typhoid fever. We humbly admit the insufficiency of diagnostic criteria and the fallibility of medical inference. And so in angina there is no warrant, simply because the diagnosis is occasionally difficult, to further perplex and confuse by claiming relationship where none exists and ignoring differences that are patent. It is time that angina pectoris be accepted at its face value and all spurious, false and pseudo anginas be abolished.

I have said that angina pectoris has a definite pathological basis. Jenner was the first to point to the relation between angina and disease of the coronary arteries. You will recall his anxiety over Hunter's symptoms and his grave suspicions which were fully verified at autopsy. Interest in the anatomical features of the disease was almost lost during the period of clinical confusion when angina meant anything from an instantly fatal disease to a flurry of nerves. Huchard revived the interest when he sought to place the disease again upon a firm clinical basis. The opening sentence of the chapters upon angina in his classical *Traité clinique des Maladies du Cœur* reads as follows: "The anatomical cause of angina pectoris is a lesion of the aorta situated near the orifices of the coronary arteries, or a lesion of the coronaries with or without aortitis, resulting in a narrowing of their caliber, a diminution or an obliteration of their lumen." To justify his view Huchard collected the records of 185 cases of angina that had come to autopsy and all of them

reported disease of the coronary arteries or of the aorta in the neighborhood of the coronary mouths. Another eminent physician, Allbutt, has more recently considered the matter in detail and comes to a somewhat different conclusion. Allbutt thinks the characteristic lesion of angina is disease at the root of the aorta. He contends that autopsy always reveals this lesion whereas the coronary arteries are often unimpaired. Although the vast array of observation and argument that Allbutt musters to support his view forces us to admit that aortitis at the root of the aorta is often the cause of angina, still the evidence that coronary disease is also frequently the cause is convincing to many. The characteristic symptoms of sudden occlusion of a branch of the coronary arteries and the great frequency of coronary thrombosis as the cause of death, are weighty arguments in favor of the view. While we must wait for fuller knowledge to decide what part is played by coronary disease in liberating attacks of angina there can be no question that the condition of these vessels is the most important single factor to determine the outcome of the disease.

Perhaps I have tarried unnecessarily long to make clear what I understand by angina pectoris even though the question has been but hastily touched upon. The course of the disease as we observe it clinically is so devious and uncertain that we cannot chart accustomed or predetermined paths. Still it will be helpful to draw a number of arbitrary divisions to facilitate description. The disease may manifest itself:

1. By sudden death in the first seizure.
2. By sudden death or death from myocardial insufficiency, after months or years of attacks.
3. By a period of attacks, followed by a long or short period of remission, then a recurrence of attacks perhaps with sudden death.
4. By a period of attacks, followed by a long period of remission during which the patient dies from some other cause. These instances are spoken of as cures.
5. By an unusually severe seizure followed by death, not sudden, but after hours or days of agony, from a gradually failing heart. The seizure may be initial or as is more often the case, follow months or years of less severe attacks.
6. By an unusually severe but not fatal seizure followed by a period of apparent recovery and months or years later by sudden death from rupture of the heart or gradual death due to advancing myocardial insufficiency.

We are then confronted by a disease which may strike with instant death in the midst of seeming health and yet from which an afflicted man may apparently recover and live on for many contented and useful years. Since any course is possible between these contrary extremes prognosis is indeed difficult and uncertain. If we were able to see clearly into the fundamental differences that distinguish

the abruptly fatal from the curable instances of the disease, prognosis would then be upon a firm basis. At the present state of our experience we are able to make only uncertain conjectures. However, a number of interesting considerations are at once suggested. Sudden death in angina is usually associated with occlusion of a branch of the coronary artery. In these instances the mechanism of the fatal issue is theoretically clear. With the sudden plugging of the vessel a large area of ventricular muscle is deprived of its blood-flow and the functional changes that must promptly follow lead to ventricular fibrillation and immediate death. There is much suggestive evidence from animal experiments and from the observation of human cases to support this view. When a coronary vessel is tied off in a certain number of instances extrasystoles develop, then paroxysms of ventricular tachycardia, then ventricular fibrillation and death. The same séquence of events has been observed in man following coronary occlusion. It is true that in animals as a rule death does not occur immediately upon ligation of a coronary artery, but when death does occur it seems always to be due to ventricular fibrillation. Instances are reported of sudden death in angina in which it is stated that at autopsy the coronary arteries and heart showed no abnormality. If we accept these data as conclusive we can give no satisfactory explanation of the mode of death. Allbutt argues in detail for a vagal inhibitory death. However, there is no experimental evidence to support the adequacy of such a mechanism.

Since angina may be due to changes at the base of the aorta as well as to disease of the coronary arteries, it seems reasonable to assume that attacks associated with coronary disease will have an ominous outlook, whereas attacks due to small sclerotic patches in the aorta will have a relatively favorable prognosis. As in other functional disturbances there is here apparently no correspondence between the extent of the pathological change and the degree of functional disorder. A small lesion may produce severe symptoms whereas extensive and sometimes extreme changes may be present in the absence of any symptoms whatsoever. There are reasons for these variations but our knowledge is too meager to elucidate them. I see no satisfactory way to explain long periods of remission, apparent cures, or the duration of recurring attacks over decades without assuming that relatively small lesions may liberate disproportionately severe symptoms. If we were able to gauge by clinical methods the seat and extent of the lesion we would be upon safe ground for prognosis. It is needless to say that we are unable to approach this desired position. We may only view it from a remote distance.

There are two common causes of aortic lesions associated with attacks of angina pectoris, infections and arteriosclerosis. Among the infections syphilis predominates. It is said that angina may follow attacks of influenza presumably due to mild aortitis which may subside. Such cases are reported but as far as I know none are

verified by postmortem examination. Many of them recover as might be anticipated if the anatomical conception is correct. Similar instances are said to follow rheumatic fever. Syphilitic aortitis is the disease above all others which produces lesions at the very base of the aorta, the location which Allbutt believes is especially concerned in the initiation of attacks of angina pectoris. As is well known the favorite site of arteriosclerotic lesions is higher up in the aortic arch. Syphilitic aortitis frequently narrows or occludes the mouths of the coronary arteries, but it rarely invades the coronaries themselves. However, in spite of this favorable location, syphilitic aortitis is relatively seldom accompanied by attacks of angina pectoris. Paroxysms of oppression with suffocation are common but these are not genuine angina. Arteriosclerotic lesions are frequently associated with sclerosis in the coronary system. Symptoms associated with arteriosclerosis occur as a rule later in life than the symptoms of syphilitic aortitis. These facts offer a satisfactory explanation for certain clinical relations of angina pectoris.

Angina occurring between thirty-five and forty-five years of age is usually due to luetic aortitis. If luetic aortitis can be excluded then the chances are in favor of coronary artery disease. In certain families a remarkable number of the males die of angina between forty and fifty years of age. In either instance the outlook is unfavorable for permanent relief from the attacks or for many years of life. Angina coming on after fifty years is usually associated with arteriosclerotic lesions. It is impossible to predict the state of the coronary arteries. However, I have the impression that cases of angina associated with moderate hypertension, with evidence of sclerosis of the aorta as indicated chiefly by the characteristic bell-like quality of the second aortic sound and perhaps with slight enlargement of the heart, are more likely to run a mild and prolonged course than are those with normal blood-pressure and normal heart sounds. Clinicians, as a rule, fear angina when examination of the heart reveals no abnormality.

In addition to attempts to fix the location of the anatomical lesion we may try to gauge its extent by functional studies. As I have said prognosis depends chiefly upon the condition of the coronary circulation and we may get some estimate of its capacity by careful inquiry into the reserve power and the recuperative ability of the heart. When attacks of angina follow slight exertion or occur when the patient is at rest the outlook for improvement is not so good as when they come only upon vigorous exercise after meals. Again, if a judicious regulation of the patient's life is followed by a cessation of attacks or a marked diminution in their frequency and severity, the forecast is better than it would be if no such obvious benefit should follow the regulation. Yet again, the response to a period of complete rest in bed is an important indication of the gravity of

the underlying process. In a word, when angina comes on in the midst of a busy, active life and the symptoms subside or greatly improve following rest or the curbing of pernicious habits, then the prognosis is good, within the limits set by the nature of the disease; on the other hand, when angina comes on with but slight provocation and persists unabated by judicious care, then the prognosis is ominous. These dicta are too terse to contain the whole truth and many flagrant exceptions may be noted. They are deductions that fit reasonably well to large groups of cases but may ill become the isolated case. Months of careful observation may be necessary to reach a satisfactory conclusion about the response of the heart to rest, exercise, worry, care, infection and the many other influences that may act upon it beneficially or harmfully. But this time is not lost nor wasted; for the guiding principle of treatment is to restrain the patient within the bounds of his functional range, and to treat him well imposes the obligation to study the functional range with all possible care.

Important help in prognosis may come from electrocardiographic studies. Certain alterations in the *QRS* complex and in the form and direction of the *T* wave are interpreted to indicate diffuse myocardial damage. Smith has shown that when in dogs large branches of the coronary arteries are ligated the amplitude of the *QRS* complex is diminished and the limbs are often notched. At the same time the *T* wave is inverted in one or more leads, is increased in size and may arise from the descendant limb of the *QRS* complex before the isoelectric point is reached. Similar curves have been recorded in man after coronary occlusion. When these electrocardiographic changes are observed in patients with angina pectoris they suggest serious myocardial damage and are therefore of grave significance. However, they cannot be interpreted in a uniform way. The changes are often transient and they may be entirely absent in patients who die soon after in an attack. Inversion of the *T* wave has been regarded as a particularly ominous sign.

Angina is always a serious disease and the outcome is uncertain. Sudden death occurs so frequently that it is looked upon with terror by the laity and with trepidation by the profession. It is but natural that this dramatic and awe-inspiring event should dominate the emotional reaction toward the disease and color it with fear. However, if the situation be regarded with calm deliberation it is not so fearful as it appears. In contrast to this tragic ending a number of palliative and reassuring facts emerge. The disease is commonly of long duration and with proper care periods of remission are the rule. These periods of remission may be so indefinitely prolonged as to simulate a cure. Every older physician will readily call to mind patients still living in active comfort about whose future he may have entertained the gravest fear ten years ago or

longer. It is both just and wise to stress this benign and favorable aspect of the disease and to hold it ever before the mind as a corrective to the overpowering emphasis of sudden death.

Sudden death in the first seizure of angina is a rare event. Perhaps it is rarer than it appears to be. I think it is because in instances of severe attacks, seemingly initial, from which patients recover, they nearly always give a clear history of preceding attacks which went unrecognized. A year ago I saw an unusually vigorous man of sixty-seven years whose youthful activity was generally remarked upon. In the midst of apparently robust health he had a terrific attack of angina due to occlusion of a branch of the coronary artery. In the light of this event attacks of so-called indigestion which he had had for five or six years preceding won a new and sinister significance. Without a suspicion of their true meaning he described graphically attacks of gas with pain under the sternum that momentarily stopped him short in the midst of exertion. I recall two of my associates carried off suddenly in the heat of a busy practice. The intimate friends of each knew of preceding warnings, warnings that did not go unrecognized by the victims.

Sudden death after months or years of attacks is not uncommon. Patients often accomplish an unbelievable amount of work in spite of ever recurring attacks. John Hunter lived for twenty years, and did much of his best work while subject to attacks. I recall a very intelligent professional man I saw on several occasions some years ago. He had severe attacks of angina and fully appreciated the gravity of his symptoms. The attacks were so frequent and alarming that his courage and endurance were undermined and he lived miserably in constant fear and apprehension. I chanced some months later to meet him casually upon the street and I was amazed at the change in his appearance and bearing. He walked briskly with firm step and head erect, the unconcerned smile of healthy vigor and confidence upon his face. He greeted me cordially and yet passed by so quickly that I could not mistake his desire to avoid further intercourse. I spoke of the change to his physician and congratulated him upon the obvious marks of his therapeutic skill. He replied that he as well as all the friends of the patient had noticed the change and commented gratefully upon it but that he could not take any credit to himself since the patient had passed from under his care. He went on to explain that the patient had embraced Christian Science and become an ardent disciple of that cult. Fortified by these strange but powerful convictions he went daily to his work and it is not hard to imagine the storms he encountered unflinchingly and without complaint. Some time later, at noon one day he left his office to go to lunch and dropped dead upon the street, as was reported, in an attack of acute indigestion. I still see from time to time a man now aged sixty-seven years who consulted me in 1916. His first attack

of angina had come on a few weeks before while running for a car and since then attacks had recurred on exertion. The physical examination was negative except for enlargement of the prostate gland. The urine contained small amounts of sugar which disappeared upon a moderate regulation of the diet. In 1918 the urinary difficulty became urgent and it was necessary to introduce temporarily a retention catheter. A year later increasing difficulty of urination forced the serious consideration of operation. Constantly recurring attacks of angina led to frequent postponement until finally the operation was successfully performed. The patient made a good recovery and has been better since although he continues to have angina when he overexerts. He is a man of large business interests and he leads a very active life.

Long periods of remission, even after severe attacks, occur frequently. One is never justified in saying that patients with angina are cured, because even though symptoms are absent the underlying anatomical lesion remains. In most instances, if the patient lives long enough, the attacks do recur. In March, 1921, I saw a lawyer, aged sixty-two years, who was having very characteristic and severe attacks of angina. He told an interesting story. In 1913 he was appointed police magistrate and was obliged to work very hard under a good deal of nervous pressure. He had always been interested in sports and had previously taken much out-door exercise, but his newly-won position necessitated abandoning this life-long habit and leading a sedentary life. He gained weight rapidly and soon began to have severe attacks of angina. His blood-pressure was taken and he was told it was very high. When the patient left the bench and again took up exercise his weight fell off and the attacks of angina disappeared. After about four years of good health the attacks came back but were not so severe as they had been before. At the time I examined him he had been having attacks at short intervals over a period of eighteen months. He refused to accommodate his habits in the slightest way to his symptoms and insisted against all advice in pursuing his accustomed activities. Two weeks later he had an appalling attack of angina due no doubt to occlusion of a branch of the coronary artery. He did not rally from this attack and died about forty-eight hours later.

Severe attacks of angina followed after a few hours or a few days by death or by recovery to end months or years later from myocardial insufficiency or rupture of the heart, are characteristic of occlusion of a branch of the coronary artery. It is only within the past fifteen years that a precise clinical picture of coronary occlusion has been drawn. Obrastzow and Straschesko in 1909 were able to find only 3 instances in which the diagnosis had been correctly made. American clinicians have added valuable contributions to the subject and the diagnosis is now relatively easy. However, the great variation in symptoms is astonishing. A number of

instances are reported in which one of the main branches of the coronary artery was found at autopsy to be occluded, although no evidence of cardiac disease had been discovered during life. There is a liberal anastomosis of the coronary arteries between the small branches of its different divisions and also with branches from contiguous vessels supplying the pericardium and the epicardial fat. If a large branch of the coronary artery is slowly occluded and sufficient time is given to allow the development of an adequate collateral circulation, the final closure of the vessel may go unmarked by any symptom. Gross has published such an instance and his beautiful photographs show an astonishing development of the rami telæ adiposæ. On the other hand if the occlusion comes suddenly the accident may be marked by the most dramatic and agonizing clinical manifestations. The severity of the shock may be estimated by the conspicuous fall of blood-pressure which nearly always accompanies it. In 1 patient following an unusually severe seizure there was anuria for over twenty-four hours. Blood-pressure observations were not made during this period but the pressure must have fallen temporarily to a point so low that the secretion of urine was interrupted. And yet, although for a week the patient wavered upon the threshold of death, he finally recovered and a year later is quite well except for some breathlessness on exertion. As observations multiply it becomes more and more apparent that death by no means always follows the accident. Indeed it appears that more instances recover than immediately succumb. In 1918 I saw a patient who three years before had had a severe attack of angina from which he recovered. He then remained well and free from attacks until twenty-four hours before my visit. While at the theater he was seized with a violent paroxysm of pain followed thirty-six hours later by pulmonary embolism. The patient was desperately ill but recovered and remained well for four years when he had the third attack which was fatal. Similar observations are being rapidly multiplied and as diagnosis improves I think we will be more and more surprised at the large number of recoveries following coronary occlusion.

Conclusion. I should like to summarize briefly the impressions I desire my remarks to leave behind them. Although angina is a serious disease often accompanied by sudden death, still it is compatible with many years of useful life and often is characterized by long periods of remission which sometimes resemble cure. We have no sure way to distinguish the malign rapidly fatal cases from the benign ones which last for a decade and longer. However, a careful consideration of the nature of the underlying process and a study of the functional range of the heart will give us valuable data upon which to risk a forecast. At present prognosis is in the stage of group prediction. As information grows we may be able to see more acutely into the differences and predict with some degree of probability the course of the disease in the individual patient.

PROGNOSIS OF THE TACHYCARDIAS.*

BY JAMES S. MCLESTER, M.D.,

BIRMINGHAM, ALA.

THE fate of the man with heart disease depends upon the integrity of his myocardium. This is just as true of those abnormal states which are accompanied by tachycardia as it is of all other forms of heart disease. Tachycardia is a mere symptom, and the prognosis depends upon the underlying disease, in last analysis upon the influence of this disease upon the heart muscle.

From an etiological standpoint rapid heart action is of three types: (1) That of purely nervous origin; (2) that which accompanies lowered myocardial efficiency, and (3) that which follows a change in the location of the pace maker.

In the first group, the tachycardias of purely nervous origin, there is no genuine cardiac disease, and the fate of the patient has little to do with his heart. Here should be included the effort syndrome. Just what factors are back of this interesting symptom-complex, whether nervous or otherwise, it is difficult to say, but we are justified in assuming that the patient's disability rests not upon lowered cardiac efficiency but rather upon the factors underlying his abnormal psychic state. It is his ability to cope with the latter which determines his fate. We can therefore dismiss from present consideration the effort syndrome and the other tachycardias of nervous origin.

In the second group, the tachycardias due directly to loss of myocardial efficiency, there are included many diseases of widely varying pathology and of all grades of severity. At one end of this group, among the diseases of less serious nature, stand those which produce so-called palpitation. In spite of its lack of seriousness it should not be forgotten that palpitation always means increased myocardial excitability, which in turn indicates some form of myocardial injury; an infection or, if you please, an intoxication.

True palpitation can be distinguished from the purely neurotic states by the short, quick contractions and accelerated conduction time. The pulse-rate rarely exceeds 150; its onset is gradual; likewise the return to normal is gradual; and it is profoundly influenced by rest. These last characteristics serve to definitely distinguish palpitation from the rapid heart action of paroxysmal tachycardia.

The prognosis in cardiac palpitation depends upon the nature of the intoxication (or infection) and upon the degree of damage done the myocardium. For example, while the palpitation seen

* Read in a symposium on prognosis in heart disease at the meeting of the American Climatological and Clinical Association, Atlantic City, May 2, 1924.

during or shortly after many infectious diseases, such for instance as pneumonia or typhoid fever, bodes little or no ill, that which accompanies certain other infections such as rheumatism is of more serious moment. Rheumatism not infrequently produces a myocardial injury which is progressive in nature and therefore of grave significance. On the other hand, when the poisoning is not of bacterial origin, such as occurs in chronic alcoholism, a cessation of the intoxication will lead usually to a gradual restoration of myocardial efficiency.

Belonging in this group is the tachycardia of exophthalmic goiter. This is an expression of the poisoning to which the myocardium is subjected. The outlook depends upon our ability to stop the process, and therefore in last analysis upon the behavior of the thyroid gland.

Another type of tachycardia is that exhibited in fibrous or fatty degeneration of the myocardium. Here the outlook is determined first by our ability to find the cause and to halt the progress of the disease, and second by the functional capacity of the remaining myocardium.

Rapid heart action is also encountered in patients with valvular cardiac disease. We should not judge, however, of the extent of myocardial strain to which these patients are subjected merely by the increase in pulse-rate which follows exertion: this may be misleading. Of more importance is a sustained rapid rate which persists even during rest, for this always indicates extremity of cardiac effort.

Often a quick pulse is the first evidence of some debilitating disease such as pernicious anemia or cancer and the prognosis is correspondingly grave. On the other hand, it should not be forgotten that a great many people live normal lives and show no signs of trouble, although there is at all times an increased heart-rate. Therefore, tachycardia alone cannot be taken as evidence of disease; the patient must be studied as a whole.

For the more accurate measurement of the cardiac efficiency of the patients of this group, numerous methods of precision have been devised, but none of these are entirely satisfactory. There is no easy way, and we must resort always to painstaking clinical observation. Of greatest prognostic importance, no matter what the cause of the tachycardia, is the degree of discomfort and distress which the patient experiences after exertion. To observe closely the manner in which the patient as a whole reacts to physical effort; to watch for signs of early exhaustion, such as dyspnea on slight exertion; and to discern other signs of myocardial weakness such as slight edema; these are the only means of detecting impending cardiac failure.

The third group of tachycardias, those in which the abnormal rate comes from abnormal origin of impulse, presents on the whole

a still graver prognosis. This group includes auricular fibrillation, auricular flutter and paroxysmal tachycardia.

Auricular fibrillation could with equal propriety be placed in either this or the previous group, for while it is dependent upon a definite change in the location from which come the cardiac impulses, it represents also myocardial disease of the gravest type. It indicates that severe strain has been thrown upon a diseased myocardium and that the heart is "in extremis."

It is sometimes of prognostic value to know how the patient deported himself before the onset of fibrillation. If he was easily exhausted and early showed other signs of cardiac failure, then fibrillation by adding to the burden of an already over-taxed heart, increases greatly the gravity of the prognosis.

The outlook, at best, in this type of disordered and irregular ventricular action is always grave, but the degree of gravity depends in part upon the nature of the disease which is responsible for the myocardial breakdown; whether for instance, it is rheumatic, renal or arteriosclerotic. If in addition to the disordered rhythm there is a continued high ventricular rate, even after rest and judicious medication, then we are justified in assuming that disaster is imminent.

The extremity of the patient's distress, his reaction to effort, and his response to treatment, as well as the signs immediately referable to the heart, such as liver engorgement and edema, offer the best criteria upon which to formulate a prognosis. The fact always remains, however, that auricular fibrillation in the vast majority of instances heralds oncoming failure and an early death.

Akin to auricular fibrillation is auricular flutter. While this condition is sometimes difficult to distinguish from paroxysmal tachycardia, the fact that it occurs in elderly individuals with arteriosclerosis and other evidences of cardiac disease, suggests a kinship to fibrillation rather than paroxysmal tachycardia. In distinguishing auricular flutter from paroxysmal tachycardia an arbitrary pulse-rate, 200 per minute, is taken as the dividing line; a ventricular rate above 200 is believed to indicate the former, while a rate below this indicates the latter. It is only by means of an electrocardiograph, however, that we can with assurance recognize auricular flutter.

The prognosis in auricular flutter, as in other manifestations of myocardial impairment, depends upon the nature of the underlying disease. Its gravity is also indicated by the ease with which the patient responds to effort, and particularly by his reaction to treatment. When, as the result of treatment, the flutter ceases, there is always an immediate improvement in his general condition. If flutter can thus be controlled by treatment the prognosis is relatively good, but if rest and appropriate medication do not terminate the flutter, then the outlook becomes extremely grave.

Paroxysmal tachycardia is accompanied by two dangers. First, the patient may die during the attack. This, fortunately, is extremely rare, and the individual attacks taken alone are usually not of great danger. Second, the attacks may become so frequent and of such long duration that they finally exhaust the heart muscle and lead to death from myocardial failure. Since no one can offer a prediction concerning this first factor, sudden death during the attack, it is the second factor, the exhaustion of the cardiac muscle, which interests us. Attacks of paroxysmal tachycardia may recur through a great many years, even decades, without serious consequence. I now have in my care a woman who has had frequent attacks of this disordered heart action for forty years, and it is only within the last few months that the heart has shown signs of failure.

The prognosis in continued attacks of paroxysmal tachycardia is in turn determined by two factors: First, the endurance of the heart muscle, and second, the severity of the strain which the heart must bear. As in other forms of heart disease, we judge of this first factor, myocardial integrity, by nothing the reaction of the patient to the paroxysms. If during the attack there are signs of myocardial failure, such as cardiac dilatation, great exhaustion, and pulmonary edema with cough, the prognosis is bad. And if to this there are added signs of cardiac weakness, between the paroxysms, then the outlook becomes especially bad. If, on the other hand, the patient stands the attacks well, and if between attacks he is able to withstand fatigue and can without too great effort undertake the work of the average individual, the prognosis is good.

When the patient is seen for the first time, something can be predicated upon the length and frequency of the paroxysms of the past and his subjective reaction to these attacks. If the attacks are increasing in frequency and severity, and if there are already present signs of beginning cardiac failure, then the outlook is bad. The patient with forty years of paroxysmal tachycardia whom I have just mentioned, is now having paroxysms of ever increasing severity and of longer duration. These attacks are now accompanied by cough and occasional edema of the lungs, and the prostration of each is profound. It would appear, therefore, that unless the quinidin, which we are now using, fulfills its promise and controls the attacks, the end is near.

Conclusion. The prognosis in the various tachycardias should be based on two factors: First, an understanding of the pathological process which causes the abnormal rate; and second, upon accurate clinical observation concerning the ease or difficulty with which the patient meets the handicap imposed by the disease.

TUMORS OF THE BREAST: A CLINICAL CONSIDERATION.*

BY JOHN F. ERDMANN, M.D.,

NEW YORK.

IN correlating material for this paper I have collected from my card index all operations upon the breast except those for mastitis, either chronic or suppurative, during the period from January 11, 1905, to and including August 15, 1923, about eighteen years, and find recorded in the index 539 cases. There were also in this series 22 carcinoma recurrence operations, which were in part mine and the remainder patients of others, one of these being operated upon four times in the scar and remote areas. Of the operated cases 315 were carcinoma, 1 of the entire number being a well-advanced bilateral manifestation. There were 141 cystadenoma, of which about 117 were unilateral and 24 bilateral; sarcoma, 2; tuberculosis, 2; lipoma, 4; aberrant breast, axillary, 3, 1 of which was carcinomatous, 1 sebaceous cyst of good size, 1 hemorrhagic cystadenoma; adenofibromata and fibrocystadenoma, 27; peri- and intracanalicular fibroma, 38, of these latter in all 65 (including intracanalicular cystadenoma and intracanalicular papilloma, etc.).

It will be observed in the figures that about 60 per cent of all the cases selected for operation were carcinoma. These operated cases do not represent by far the patients seen with cystadenomatous degeneration of such slight degrees as to be considered non-operative. Neither does the large number of cystadenomatous breasts operated upon represent an evidence of operative furor in this class of pathology, but they were in all instances patients with this type of degeneration so far advanced as to demand operative relief. Numbers of them had had single cyst operations done on various occasions, one in particularly asking for radical relief after five individual operations had been done by various operators, each operation being guaranteed as being the last of her trouble.

It has been my experience to see but 2 tuberculous tumors and 2 sarcomata in this period of time and 1 aberrant breast undergoing malignancy, which finally required a reoperation, including the previously normal breast.

There are 4 instances in the carcinomata in which the second breast was invaded. One of these patients was inflicted with the second growth so remotely placed from the chain of lymphatics as to lead me to consider the tumor of primary origin, equal to that of the first breast. There was 1 bilateral carcinomatous involvement almost equal in both breasts. The case is so interesting as to deserve recording.

* Read before the Springfield, Mass., Academy of Medicine, December 11, 1923.

CASE HISTORY.—C. M., aged forty-seven years, single, was admitted to the New York Post-Graduate Hospital, March 17, 1921; discharged, March 28, 1921.

Chief Complaint. Tumors of the breast, duration seven months.

Family History. This was negative, as was the past history. There were no operations and no previous illness of moment.

Personal History. The menopause occurred two years ago, with some slight spotting since.

Present Illness. Began seven months ago, without pain and with no discharge from nipple. There was no loss in weight.

Surgical Condition. There is a definite assymetry of the two breasts. The left presents a flattened-out and retracted nipple. The entire breast is hard, rubber-like in consistency. It moves as a whole on the chest. There is a large hard gland in the axilla, freely movable and smooth. The right breast is very hard, especially about the nipple. There is no retraction of the nipple, but the skin retracted in other areas and very adherent to the underlying tissues. There are a few very small hard nodes in the axilla.

Operation. Bilateral Stewart incision; result: primary union.

Pathological Report. Bilateral scirrhus carcinoma, with metastasis to lymph glands.

The pericanalicular and intracanalicular tumors were seen in the female, usually from seventeen to thirty-five years of age. The cystopapillomata, of which quite a few were recorded, were easily diagnosed at the first visit by the characteristic discharge from the nipple. In the non-recorded cases of mastitis, I am quite satisfied that 3 recently operated upon were fat necrosis cases of the type described by Burton Lee. In neither of these did I remove more than the areas involved.

As to the question of bilateral involvement being primary or of the second breast being invaded through lymphatic conveyance, one is unable to decide, but I am rather fixed in my opinion as to 2 of the patients specially cited. In the instance of the patient with the immediate bilateral involvements I am inclined to believe after very careful examination and cross-examination that the breasts were simultaneously invaded by primary growths, or almost so; at least I feel that neither growth was a metastasis from the other.

In a patient with involvement of the remaining breast four years after the removal of the absent breast, the zone occupied, the discrete type of tumor, absence of any infiltrating process from the removed side and the absence of evidence by roentgen-ray of any other metastases, lead me to a positive conclusion that involvement of the remaining breast was as much of a primary growth as the tumor in the removed breast. Unless we can definitely trace the metastatic chain across the breast, such instances as the one just cited should be classed as primary and not as metastatic.

In this series of patients but 3 were in the male, 1 a recurrence and 2 primaries. I have previously reported¹ on 3 male patients with tumors of the breast.

Diagnosis of Malignancy. The most frequent reason, barring the presence of a tumor, that patients advance for suspecting malignancy is pain. It is most gratifying to be able to tell these worried callers that malignancies of the breast never begin with pain, that when pain is a symptom of cancer it requires no expert to diagnose the condition and that the pain in these patients is due to compression involvement of the nerve filaments, infiltration, or a large tumor, or exposed nerve filaments in an ulcerating tumor. As a rule, malignancy of the breast is a single tumor, as compared with multiple tumors in cystadenoma or fibroma, although one occasionally sees a malignancy present with a well-defined multitumor not of the cystic variety. Recently I have removed a carcinomatous breast with two distinct nodules, 4 inches apart. The bilateral breast tumors are most frequently the cystadenomata and fibromata.

No better diagnostic objective evidence is known than the dimpling of the skin when the breast is grasped, as compared with the full rounded convexity of the normal breast when compressed between the examining fingers. This dimpling sign of malignancy is obtained very early. By lifting the breast from below, or by compressing it between two or more fingers, the dimpling will readily follow, while in the non-involved breast the convexity will remain or be exaggerated. This dimpling can also be seen without difficulty either by direct or by oblique inspection, and by feeling carefully over the dimple one obtains with the palpating hand the sense of hardening or tumor. In patients with more advanced, or in patients with a more disseminated growth, the classical orange-peel skin is seen. The elevation of the breast affected above the plane of the other, due to the lifting effect of the involved tissues, is seen in more advanced conditions. Strongly abducting the arm from the side, thereby making the skin and pectoralis major tense, will often bring the tumor into bold relief. Compression of the breast upon the chest wall, with the patient prone or in erect posture, is an excellent means for detecting irregularities of the breast.

Retraction of the Nipple. If one were to rely upon this condition for a diagnosis operations upon the breast would be more common than those for the appendix. In a very large proportion of patients there are single or bilateral retracted nipples in breasts that are absolutely normal otherwise. The retracted nipple of malignancy is due to the same cause as the dimpling of the skin mentioned above. Eversion of this latter type of retraction is usually impossible, while in the normally retracted nipple eversion is quite possible in the great majority.

¹ Dennis: System of Surgery, 1896, 4, 944.

Axillary Adenopathy. To be found readily on palpation in the majority of patients, it requires an exceptionally enlarged gland, or an exceptionally thin subject is essential.

Metastases. These are important in their bearing upon the question of operative justifiability. One cannot be too careful in the readily palpable tumor in the search for secondaries, those of the mediastinum or lungs, characterized by a dry cough; in the bones by pain allied to nerve distribution pains, such as facial, intercostal and, in my experience, frequently in the course of the sciatics, one or both.

One of my patients lived eleven years after a very extensive dissection. The first evidence of metastasis was a hoarseness of voice, increasing slowly in intensity. It was not suspected that the hoarseness was in any way due to metastasis from the growth removed almost eleven years before until roentgen-ray showed a tumor, the shadow of which was the size of a tangerine and situated above the arch of the aorta.

As far as my personal observations go, I cannot encourage the idea that metastases occur in the abdominal viscera in such frequency as we are lead to believe by various observers. Therefore, I am not inclined, in all patients, to practise Handly's resection of the upper segment of the rectus fascia, although I frequently do it.

In addition to the remote sites mentioned, the immediate sites call for consideration. Recurrence in the scar can be assigned to too small a skin-flap removal; implantation by the using of forceps in the flap edges that have not been properly cleaned after use in the ablated portion; the conveying of cells on the gloves, towels, sponges and other instruments, that have been in contact with the removed area. The fact that cells may be lodged in the lymphatic channels at a remote area must account for those shot-like bodies seen later at a distance from the scar of operation. Occasionally the shot-like masses in the area formerly occupied by the breast are cystic formations about a ligature, and will disappear in time.

No breast should be removed when the supraclavicular and cervical glands are so metastatically enlarged as to be readily palpated, but should be subjected to roentgen-ray or radium for some time. This same statement holds in those patients with massive skin infiltration. I have recently had a marvelous disappearance of the skin infiltration in a woman, aged thirty-eight years, after roentgen-ray application by the more recent high voltage machine, although the tumor proper maintained its original size after six months' treatment. This patient was subsequently operated upon and died in six months, even with added postoperative roentgen-ray exposures. No breast should be operated upon with a promise of cure or a great extension of life in which the growth, ulcerated or not, is adherent to the chest wall. This type should also be sub-

jected to radiotherapy, exceptions being in the instances when one can remove the ulcerating tumor and cover either by plastic or by grafting processes.

I believe that tumors, when they are small, should be operated upon, and not treated by roentgen-ray until after operation. A regrettable incident occurred in my practice in 1921. A patient with a small nodule in the upper inner quadrant of the right breast was advised by me to be operated upon. However, she had a relative connected with a large hospital, which deals largely with malignancies, and is well furnished with radium and roentgen-ray appliances. By this overenthusiastic relative, the patient was given every confidence of cure, and I lost sight of her for six months. Upon her return to me at the end of this period, during which, she stated, she had been told that she was cured, the growth was still present, decidedly larger and, in addition, there was distinctly evident adenopathy. Operation was again advised and consent at this time given. The removed growth was carefully examined by a pathologist, and no cell changes, due to roentgen-ray "sickening" or destruction, was observed by him.

Recurrences may be exceptionally rapid, and again very slow. The explanation for either is not ordinarily obtained from the pathologist. At times he will predict rapid recurrence, as was done in the case of the patient with mediastinal growth eleven years after the operation. This patient was considered by two pathologists to be liable to a rapid, six- to twelve-month, recurrence, and without roentgen-ray or radium treatment lived eleven years before showing a suspicion of a secondary tumor. No autopsy was done in this case, so that even with the roentgen-ray picture we are still in doubt as to the nature of the growth. Recently I have been notified of the death by senile dementia of a former patient of mine from whom I removed a breast sixteen years ago. The prognosis made by the pathologist was that of a rapid return. No evidence of a recurrence was observed, however, by her last attending physician. The youth of a patient, as in cancers at any site, is a strong factor in early or rapid recurrence or metastasis. The zone of the tumor, I am led to believe, may also be a factor in rapid metastasis. My most rapid recurrences under this heading are secondary to tumors in the axillary border of the breast, and also in the fat type of patient more frequently than in the lean.

The question of doubt in diagnosis may in most instances be determined by an immediate pathological examination of a frozen section. I do not believe that a wide resection of a growth for immediate analysis endangers the patient at all. I cannot make the same statement for those patients in whom the specimen is removed days or weeks before the breast is removed. The clinical picture on gross section of these questionable growths is, as a rule, so clear that the experienced operator in the majority of instances does not require the microscope except as a confirmatory measure.

Roentgen-ray or radium as a preliminary to operation is, in my opinion at the present time a "follow-the-leader game" that will require some years to satisfy us definitely as to its practicability. Use of these agents subsequent to operation is today largely enhanced by the advertisement the agents have received in the public press and by the friends of the patient. I am at present compelled to say that my cases longest free from metastasis were not treated with roentgen-ray, as at that time roentgen-ray and radium were not in their present-day positions.

To be effective in the prolonging of life or producing a cure, at present the most painstaking and extensive dissections are necessary. I am unfortunate in this discussion in being unable to bring before you statistically my recurrences as to site and time, as but forty-three replies were received to one hundred and fifty questionnaires sent. Neither am I going to entertain the question of pathology. The most radical operation consists in the complete resection of the pectoral muscles, cleaning out of the axilla of glands and fat, and extending the excision at times to the supra-clavicular space. I do not demand the removal of the pectoralis minor, except when unable to freely approach the vessels and nerves of the axillary and subclavicular zone. No functional disturbance follows the removal of both pectorals, therefore no hesitancy in removing them should exist.

The questions to be considered in a breast amputation must be: Is it justifiable from the standpoint of recurrence or metastasis? Is the mortality chance sufficiently low? Will the functions of the upper extremity after operation be preserved? The answers to two of the preceding questions are self-evident as a rule.

The functions of the upper extremity should never be involved. Free motion is always possible when orders for motion are properly carried out in practically every incision devised. The greatest impairment of motion may arise in the Willy Meyer-Halsted incision of years ago, where the axillary edge of the pectoralis major is followed. This line of incision when healed has to be stretched when abduction is instituted, and therefore in the nervous and hypersensitive individual limitation may be the result. If, on the other hand, the modified incision be used in which the incision slopes gently over the deltoid with convexity upward, when the arm is abducted the points of origin and termination of the incision are brought together. The Stewart incision has been used in over 85 of my patients since 1916, with no great difficulty in exposure and no great obstruction to motion after the first few weeks, although many patients complain that the upward (abduction) movement drags on the chest wall scar in the early period following operation. The advantage of this incision is purely cosmetic, and should be used in selected cases only.

The mortality in my carcinoma cases was 2, and these deaths

were partly attributable in all probability to a siege of *Streptococcus hemolyticus* infections that we had in the hospital at that time, also in 1 of these patients due to a second operation being done within eight or nine days subsequent to the first. This patient refused anything but a removal of the suspicious growth and demanded waiting for eight or nine days after being told that the pathological report was carcinoma. On operating radically, the area from which the tumor had been removed was found filled with clot and the surrounding tissues ecchymotic. A complete removal was done, a rapid rise in temperature to 103° F. in two days, purulent metastases were observed all over the body, joints and cellular tissue, with death resulting in ten days. Culture returns from the pus at the various sites was always that of *Streptococcus hemolyticus*.

It is very pleasing to record relatively few chest complications in so large an area of exposure to trauma and infection in the respiratory zone.

Cystadenoma, single cyst, or the blue-dome cyst of Bloodgood, cystofibroma, multiple cyst, intracanalicular, pericanalicular, or adenofibroma, are, as a rule, readily diagnosed.

In the cystadenomata and multicystic breasts one feels a single or many small nodules. Very often careful massage from the periphery to center will cause to be extruded from this nipple a fluid varying in consistency and in color from watery to pale straw, purulent or milky, bloody or chocolate-brown appearance. In all but the bloody or chocolate-colored fluids one can safely say that he is dealing with a benign condition. This type of growth is also prone to be bilateral. Recently I removed the remaining breasts of 2 women previously operated upon, the one nine years and the other six years, for the same disease. Among its many names, the term "old maid's breast" is frequently applied. When the discharge is bloody or chocolate-colored the diagnosis is usually that of intercanalicular papilloma or a papillomatous cystadenoma. Again, this bloody type of discharge may be due to bleeding from a non-papillomatous cyst with a malignant growth in the wall of the cyst. In the latter instance the precautions taken in a definite malignancy had better be observed. By careful palpation one is often able to outline a tumor in the area circumscribed by the outer margin of the areola and usually close to the nipple. On section of this tumor the eye frequently sees the cockscomb-like papillomatous growth. These processes usually grow from the inner wall of one of the larger ducts. The question of these papillomata being malignant is disputed by many. I believe that a papilloma of the breast is as dangerous as a papilloma of the bladder or rectum, and that, therefore, radical removal is in order, at least the removal of the breast is demanded.

In an article published by me² I called attention to this type of tumor, recording a series of 17 patients, with several illustrations taken from the removed breasts, presenting very typical papillomatous growths, and cited the work of A. A. Strasser, Arlington, N. J., who credits Bowlby³ with being the first to use the term duct papilloma. I further stated that the question of malignancy in the early stages can be answered in the negative, but that they do become malignant, as evidence, Greenough and Simmons report 14 per cent in the pedicles and Bloodgood at that time claimed 50 per cent in the cases observed at the Johns Hopkins. My conclusion in this quoted article was that in small growths excision of the growth suffices, while in larger growths amputation of the breast is imperative. I shall modify this now by saying that I feel that all papillomatous breasts should be amputated.

Intra- and Pericanalicular Fibroma. In 1 instance a very large growth involving the left breast, weighing 5 pounds, was removed, the clinical diagnosis of which was sarcoma, the pathological that of an intracanalicular adenofibroma, with no gland invasion. Complete removal was done. Six months later the patient coughed up a piece of tissue. Pathological diagnosis was sarcoma. At about the same time the entire cutaneous area was involved with growths from the size of a French pea to a hazelnut. These were subsequently pronounced sarcoma. The inference is either that the slides were wrongly read by the first pathologist or that the original canalicular growth degenerated into a sarcoma at some point that escaped the pathologist's attention.

As previously stated, my list of operations for cystic breasts does not represent an operative furor: These operations were done for demand reasons—persistent soiling of the linen by leakage; rapid growths; reoperative disappointment and fear of more operations on the part of several who had from two to five removals done which were followed in a short time by palpable recurrences or rather new growths. These in all probability were preëxisting small cysts that enlarged.

In those patients in whom we intend removing a single cyst, but whose breast tissue we find studded with numerous cysts in size just visible to that of a French pea or larger, I advocate amputation of the breast without the extensive dissection done in malignancies.

These patients do not have the feeling of mutilation, as expressed by Bloodgood, and more recently by Peck quoting Bloodgood, but in the majority of instances are grateful for the work done. I feel that if they are to have the operation created in their minds many times by propagandists and annual cancer weeks, newspaper notoriety and so on, that a placid mentality due to a complete operation is far better than diseased mentality with a less radical

² Am. Jour. Surg., 1912, 26, 208.

³ St. Bartholomew's Hosp. Repts., 1888.

operation, not only for the tumor-bearing individual but also for each of her relatives and friends.

While cancer-week notoriety and propagandism is desirable, nevertheless I have found from my office experience that a great deal of unnecessary mental suffering is created during these periods which again is followed by the gratitude of the sufferer whose mind is relieved.

In the single growth, the blue-dome cyst of Bloodgood, the discrete fibroma and the canalicular growths, the operation of removal resolves itself into a resection of the area well outside the tumor, with proper suture repair.

Conclusion. In conclusion I should like to emphasize the belief on my part.

1. That no tumor in the breast is a desirable tenant, even if its innocence be proven without a question of doubt.

2. That a growth in the remaining breast is as likely to be of primary origin as was that in the breast first removed.

3. That at the present day we are unable to state positively what the influence of roentgen-ray and radium is either as a preoperative or postoperative aid. But in view of many apparent reductions in size, previous to operation in cases considered non-operable, the use of roentgen-ray and radium should be encouraged until proven a menace. In my opinion too few years have passed for positive results to be shown even in view of some of the glowing reports at present regarding the non-recurrence. Postoperative treatment should not be neglected by preoperative until some definite proof of its help or inefficiency has been established.

4. That in the presence of late metastases the powerful currents of the present day should be given a thorough test to prove or disprove the efficiency of this method of treatment.

5. That the most thorough and painstaking wide removal with remote glandular and fascial dissections will tend more and more to increase our percentage of cures and extension of life. That the radical operation is attended with so low a mortality as to promote a greater desire on the part of consulting physician to demand early operation.

THE RESULTS OF OPERATIONS FOR CHRONIC APPENDICITIS (SECOND SERIES.)

BY CHARLES L. GIBSON, M.D.,

SURGEON TO THE FIRST (CORNELL) SURGICAL DIVISION, NEW YORK HOSPITAL,
NEW YORK.

THIS paper is supplementary to one published in this Journal in 1920,¹ which set forth the results of operations for chronic appendi-

¹ AM. JOUR. MED. SCI., 1920, 159, 654.

citis in my ward-service of the New York Hospital from January, 1913, to July, 1919. In that paper it was pointed out that we had too large a proportion of unsatisfactory results. It was, however, shown that better results were obtained in the last year and that the earlier results fell into a period of reorganization and the preparation for and active participation in the World War. The better results began to show so soon as we were able to analyze the causes of our failures and apply better methods.

TABLE I.

Year.	Number of cases.	Unsatisfactory, per cent.
IODIN PREPARATION.		
1913	70	28
1914	63	23
1915	98	28
1916	100	26
1917	119	24
1918	84	20
PICRIC ACID PREPARATION.		
1919	68	13
1920	97	19
1921	105	6
1922	126	7
1923	79	8

This second series represents a period of stability and an earnest endeavor to improve our methods. It has been most satisfactory to find that the beginning improvement noted in our first paper has been maintained and improved, and we have only 9 per cent of unsatisfactory, a 50 per cent improvement.

Our results have been studied with careful attention to the lessons of our follow-up system which has now been in operation eleven years. This last series shows only 5 per cent without follow-up report, a remarkable showing for a hospital service with many recent immigrants who quickly scatter. Table II gives a comparison of the results.

TABLE II.—COMPARISON OF THE TWO PERIODS.

Results.	January 1, 1913, to July 1, 1919.		July 1, 1919, to January 1, 1924.	
	No.	Per cent.	No.	Per cent.
A. Excellent	259	46.0	283	62.0
B. Satisfactory	65	12.0	105	23.0
C. Unsatisfactory	102	18.0	41	9.0
D. Unknown	126	23.0	22	5.0
E. Deaths	3	0.5	3	0.7
Total	555		454	

NOTE.—In the second series the unsatisfactory results have been cut down 50 per cent.

Our routine procedure comprises a reëxamination by the operator in person after three months. Whatever the result, the patients are told to come back any time they like if they have any complaints, so some of our notes extend over a period of years. Patients with definite complaints (Class C—Unsatisfactory) are usually urged to reënter the hospital for examinations, fluoroscopy, cystoscopy, and so forth. Some of these are relieved by the hospital stay alone, suitable diet, laxatives and suppression of bad liquor; but are still recorded in the unsatisfactory class although subsequently reporting themselves all right.

To get an accurate classification we have adopted a standard, which is in a measure unfair as it gives an exaggerated value to irrelevant complaints.

Class A, Excellent, applies only to patients who make absolutely no complaint; a condition hard to attain, as many of these people are naturally a discontented and complaining lot.

Class B, Satisfactory. The patient has some complaint; but not directly connected with the operation, *e. g.*, constipation, a normal condition for these sedentary sweatshop workers.

Class C, Unsatisfactory. All those having definite complaints, even if we believe they are liars or neurotics, as many are. For instance a girl fat and rosy, who has gained forty pounds; but claims to vomit daily, is included in this class.

In the first paper I formulated the following rules: "To avoid disappointing results after operations for chronic appendicitis, I recommend:

"1. A comprehensive and detailed history.

"2. A complete and thorough physical examination, including all refinements of diagnosis.

"3. Exercise caution in undertaking operation on women as compared to men.

"4. Exercise caution, particularly in the more mature patients, particularly women. In this class other lesions may coëxist or may be mistaken for appendicitis.

"5. Avoid the neurasthenics of any age or sex.

"6. Exercise particular restraint when there is no clear and reliable history of well-defined attacks, particularly of localized pain accompanied by nausea or vomiting.

"7. Make a good-sized incision, and, even if a frankly pathological appendix is found, look for other possible lesions.

"8. If no obviously pathological appendix is found, do not cease looking for other lesions until every other possibility has been exhausted; make a supplementary incision if necessary."

From a study of the second series we feel we have nothing to take back in these conclusions, and while essentially no new knowledge has been acquired, the value of the rules has been emphasized. Table III gives comparative statistics of some of the main lines of observation.

TABLE III.—COMPARISON OF TWO PERIODS.

Items analyzed.	Percentage.							
	Excellent.		Satisfactory.		Unsatisfactory.		Unknown.	
	1919.	1924.	1919.	1924.	1919	1924.	1919.	1924.
A. Male	70.0	69.0	14.0	17.0	16.0	9.0	..	5.0
Female	56.0	58.0	16.0	26.0	28.0	11.0	..	5.0
B. History of well-defined attacks	51.0	47.0	51.0	48.0	35.0	18.0	47.0	41.0
C. Kind of incision:								
McBurney	37.0	1.0	22.0	0.0	31.0	0.0	52.0	0.0
Large	63.0	99.0	78.0	100.0	69.0	100.0	48.0	100.0
D. Average number of days spent in hospital	2.6	1.7	2.5	2.1	3.2	2.2	2.3	1.4
E. Special examinations	46.0	17.0	54.0	24.0	56.0	36.0	36.0	18.0
F. Appendix diseased	85.0	96.0	75.0	95.0	63.0	84.0	77.0	90.0
G. Further exploration	52.0	80.0	83.0	89.0	73.0	84.0	52.0	90.0
H. Subsequent admission	2.0	2.0*	0.0	0.9*	25.0	32.0	2.0	0.0
I. Subsequent operation	1.5	1.0*	0.0	0.0	5.0	4.0	2.0	0.0

* Admitted and operated on for conditions in no way related to appendix, *i. e.*, cellulitis of foot.

Of the unsatisfactory cases, 32 per cent were male and 68 per cent were female.

Total number of male cases, 164. Of this number, 14 cases (9 per cent) were unsatisfactory. Total number of female cases, 290. Of this number, 30 cases (11 per cent) were unsatisfactory.

Total number of unsatisfactory cases, 44. Of this number, 14 cases were male (32 per cent); 30 cases were female (68 per cent).

Item A. It will be noted that women continue to give the most unsatisfactory results. This fact we knew from our earliest studies and tried diligently not to fall into this obvious trap. We feel that the proportion of so-called chronic appendices in women should be diminished to approximate more nearly the ratio of operations for acute appendicitis in the two sexes.

Item B. Shows the importance of a definite intelligent history of previous attacks. In our latest series of unfavorable results (Class C), only 18 per cent gave this clear-cut picture.

Item C shows the disappearance of the McBurney incision, all our operations permit of thorough exploration.

Item D shows that patients were kept longer under observation for the same reason as given in item E.

Item E shows that more examinations were made in the unsatisfactory (fluoroscopy, cystoscopy and so forth), these being the cases in which the clear-cut histories were wanting.

Item F bears out the observation of our first series, that in the unsatisfactory cases the appendix is less often recorded in the operative dictation as being distinctly pathological. We have, however, a gratifying increase, 84 per cent, over 63 per cent of our first series.

Item G shows the great increase in the amount of exploration as recorded in the dictation of the operation in our second series—made possible by a proper incision. This is probably a most important factor in the improved results.

Item H shows that an important percentage of our unsatisfactory results were readmitted for investigation or treatment; but item I shows that only in a very small percentage were indications for another operation established.

A comparison of the postoperative complaints of the Class C patients (Table IV) shows no essential difference in the two periods (102 cases in first period, 41 in second). Pain of some kind is the constant complaint. Pain of course is hard to check up; we have no means of denying or corroborating the patient's story. One feature that is disconcerting is the percentage of these Class C patients complaining of the "same pain as before operation" (19 per cent for 1919, 43 per cent for 1924). The complaints fall into two main groups, same pain as before operation and gastro-intestinal complaints.

TABLE IV.—POSTOPERATIVE COMPLAINTS OF UNSATISFACTORY CASES.
CLASS C.

Same pain as before operation (4 male and 14 female)*	18
Gastro-intestinal complaints (3 male and 9 female)	12
Pains everywhere	2
Numerous complaints	2
Gynecological conditions	4
Pain in upper right quadrant	1
Pain in upper end of scar and sometimes around ribs and chest	1
Pain over kidney region	1

* Same pain as before operation, 1st series, 1919, 19 per cent; same pain as before operation, 2d series, 1924, 43 per cent.

Class D, Unknown. There was a gratifying decrease in this class in the second series.

Class E, Deaths. (Three cases in second series).

CASE I.—L. C., male, aged thirty-four years. Appendix diseased. Exploration negative. Developed consolidation at the base of the left lung. Transferred to the Medical Side. Temperature began to remit and condition of patient became quite satisfactory. On the fourteenth postoperative day he suddenly developed dyspnea and complained of a pain in his chest. Died in five minutes. Autopsy showed embolism of pulmonary artery, thrombosis of right internal iliac and infarct of lung.

CASE II.—A. S., male, aged thirty-four years. Appendix not diseased and exploration negative. Convalescence uneventful until ninth postoperative day when the patient got up. He became

cyanotic with great air-hunger and died in fifteen minutes. Autopsy showed thrombosis in left internal iliac with a pulmonary embolus at the bifurcation of the left pulmonary artery.

CASE III.—H. D., male, aged thirty-five years. Appendix diseased. Exploration negative. On the second day following operation the patient began to have acute pain and signs of peritonitis. Revision of first operation: diffuse peritonitis. The source could not be ascertained. Jejunostomy and drainage. The patient died shortly after leaving operating room. No autopsy.

Summary. Attention was called in our first paper to the coincidence of our beginning better results with the replacement of tincture of iodine by picric acid as a skin disinfectant, introduced in the last half of 1918 and continued to date. We believe it may be a feature (perhaps important) of our continued improvement, as it is less irritating and less easily carried into the peritoneal cavity.² We note it is coming more into general use.

We believe that unsatisfactory results in surgical practice may be greatly diminished if the will to do better work is established. We believe that a most important factor is the creation of a workable standard on which to base results, a careful analytical study of the causes of poor results and the unflagging desire and search for better methods. If these requirements are fulfilled, better results will more than repay all extra effort.

THE PRESSURE FACTORS IN THE BILIARY-DUCT SYSTEM OF THE DOG.

BY A. WINKELSTEIN, M.D.,

AND

P. W. ASCHNER, M.D.,

NEW YORK:

(From the Surgical Laboratories of the College of Physicians and Surgeons, Columbia University.)

Introduction. The mechanism effecting the intermittent discharge of bile into the duodenum of man is a problem of great interest. Many of the factors involved have been subjected to experimental study in the dog whose biliary system resembles closely that of man.

² Gibson, C. L.: The Advantages of Picric Acid over Tincture of Iodine for Disinfection of the Skin, *Ann. Surg.*, 1919, 69, 127. Farr, C. E.: Picric Acid in Operative Surgery, *Ann. Surg.*, 1921, 73, 13.

The part which the gall-bladder takes in this mechanism is the chief point of the divergence of opinion in such experimental studies.

Recently one of the authors concluded from the result of experimental studies^{1, 2, 3} that the intra-abdominal pressure seems to be the most important agent in effecting the flow of bile from the gall-bladder into the duodenum of the dog. Apparently the entire problem of the biliary flow is bound up with the question of the differential pressures existing in the biliary system. For instance, it is not enough to know that the gall-bladder has tonus variations or that its musculature is capable of contracting on its contents. The question is whether the pressure obtainable is actually large enough to expel part or all of its content. In other words the quantitative variations in the pressures existing in various parts of the biliary system and their relations to each other form the problem of the mechanics of the biliary drainage.

We have attempted, therefore, to study these various pressures experimentally considering: (a) The common and cystic ducts, (b) the sphincter of Oddi, (c) the gall-bladder; (d) reciprocal or contrary innervation, and (e) the intra-abdominal pressures. The experiments will be briefly recorded.

The Pressure in the Common Duct. *Experiment 1.* May 24, 1923. Young female dog (3257), weighing 7 kilos; ether anesthesia; cystic duct tied. A small glass T cannula was placed in the common duct, and connected with an upright calibrated manometer.

Readings: 60 to 65 mm. bile.

Pilocarpin, gr. $\frac{1}{12}$ given subcutaneously and observations taken for a half hour.

Readings: 60 to 70 mm. bile.

Experiment 2. Same animal. Abdominal wound closed tightly about the upright manometer and respiratory fluctuations noted. Types of respiration imitated by varying the depth of the anesthesia and by manual compression of the lower thorax and abdominal wall. (a) Shallow respiration: fluctuation in the height of bile column, 3 mm.; (b) Forced respiration: fluctuation in the height of bile column, 6 mm.

Discussion. It is apparent that the pressure in the common duct is rather low; furthermore this pressure varies little, being only slightly influenced by pilocarpin and respiration.

The Tonus of the Sphincter of Oddi. *Experiment 3.* May 4, 1923. Male dog (3323), weighing 13 kilos; ether anesthesia. A cannula, directed toward the duodenum, was placed in the common duct and connected with one arm of a calibrated manometer. To the other arm was attached a syringe filled with warm normal saline,

¹ Winkelstein, A.: Klin. Wchnschr., 1923, 2, 406.

² Winkelstein, A.: Ztschr. f. Exper. Med., 1923, 24, 127.

³ Winkelstein, A.: Jour. Am. Med. Assn., 1923, 80, 1748.

dyed with methylene blue. This apparatus is similar to the one recently used by Mann and Giordano.¹

The duodenum was opened by a longitudinal incision opposite the papilla of Vater. The colored saline was forced up in the manometer until a drop appeared at the papilla. Readings were taken. Various substances were placed in the duodenum on the papilla, allowed to remain there five minutes, and then aspirated. Following the readings, the papilla was flushed with warm normal saline.

TABLE A.

Substance.	Where applied.	Pressure (saline, mm.).
Normal contents	Duodenum	330
Normal saline	"	330
Magnesium sulphate (25 per cent)	"	220
Hydrochloric acid (N/10)	"	330
Glucose (2 per cent)	"	240
Peptone (1 per cent)	"	240
Cottonseed oil	"	220
Bile salts (10 per cent)	"	260
Benzyl succinate	"	260
Potassium carbonate (10 per cent)	"	160
Calcium chlorid (10 per cent)	"	460
Adrenalin (1 cc, 1 to 2600)	Subcutaneously	150
Pilocarpin (gr., 1/12)	"	250
Atropin sulphate (gr., 1/100)	"	100

Experiment 4. May 11, 1923. Young female dog (3339), weighing 15 kilos. Procedure as in Experiment 3.

TABLE B.

Substance.	Where applied.	Time (minutes).	Pressure (saline, mm.).
Normal contents		20	135
		2	130
		4	115
		6	105
		8	100
Adrenalin (1 cc, 1 to 2600)	Subcutaneously	10	102
		15	108
		20	105
		25	128
		30	134
		2	132
Atropin sulphate (gr. 1/100)	Subcutaneously	4	130
		6	110
		8	115
		10	110
		15	135
		20	135
Magnesium sulphate (25 per cent)	Duodenum	23	137
		3	118
		6	110
		9	120
		12	125

¹ Arch. Surg., 1923, 6, 1.

Experiment 5. May 18, 1923. Young male dog (3348), weighing 9 kilos. Procedure as in Experiment 3.

TABLE C.

Substance.	Where applied.	Time (minutes).	Pressure (saline, mm.).
Normal contents	Duodenum	20	110
Pilocarpin (gr. 1/12)	Subcutaneously	2	115
		4	120
		6	125
		8	125
		10	130
		15	110
Atropin sulphate (gr. 1/100)	Subcutaneously	1	115
		3	110
		5	105
		6	105
		8	110-120

Experiment 6. June 7, 1923. Young female dog (3382), weighing 10 kilos. Procedure as in preceding experiment.

TABLE D.

Substance.	Where applied.	Time (minutes).	Pressure (saline, mm.).
Normal contents	Duodenum	20	140
Magnesium sulphate (25 per cent)	Duodenum	5	120
		10	125
		12	125
		14	115
		16	110

Discussion. (a) Concerning spontaneous variations in the tonus of the sphincter. These are apparently slight as evidenced by the constancy of the repeated readings for fifteen to thirty minutes at the beginning of each experiment. Furthermore, the sphincter shows a tendency to return quickly to its original tonus after a stimulating or inhibiting influence has been exerted.

(b) Concerning foodstuffs. The substances usually present in gastric chyme (fat, dextrose, peptones) reduce the tonus when placed on the papilla of Vater.

(c) Concerning certain chemicals. Magnesium sulphate, potassium carbonate, and bile salts, lessen the tonus when placed on the papilla of Vater. Calcium chlorid increases the tonus.

(d) Pilocarpin increases, while atropin and adrenalin decrease sphincter tonus when administered subcutaneously.

(e) It seems difficult to lower the tonus of the sphincter very much. In most cases, the reduction averaged only one-sixth to one-fifth of the original figure. The lowest reading in any case was 90 mm.

The Cystic Duct. It has been suggested that the spiral valves of Heister, present in the cystic duct, may offer an appreciable resistance to the entrance and exit of bile. This was investigated

by Mann¹ who found that these mucosal ridges cause only a maximal resistance of 30 mm. of water. One of the authors² observed that when the common duct in a dog under ether anesthesia was cut across, a pressure on the gall-bladder merely of 15 mm. of water was sufficient to express bile through the cystic duct. It was thought unnecessary to repeat these experiments.

The Tonus of the Gall-bladder. In these experiments it was attempted to obviate as possible sources of error, the influence of respiration, circulatory changes in the liver, and the varying amount of bile entering the gall-bladder, by stripping the fundus of the gall-bladder away from its liver bed and carefully ligating the cystic duct without tying off the cystic artery. The following experiment (Experiment 7) demonstrates the disturbing influence of respiration when the fundus is not stripped from the liver.

Experiment 7. May 24, 1923. Young male dog (3357), weighing 7 kilos; ether anesthesia; calibrated upright glass manometer attached to a cannula in the gall-bladder. The fundus was not stripped from the liver and the cystic duct was not ligated.

Readings:

	Expiration (bile, mm.).	Inspiration (bile, mm.).
Cystic duct open	25	40 to 45
Cystic duct closed by ligature	15	20 to 25
(Observations for a half hour.)		

Pilocarpin, gr. $\frac{1}{12}$, given subcutaneously.

Reading fifteen minutes later: 60 mms. of bile. (At expiration, cystic duct occluded.)

Experiment 8. July 26, 1923. Young male dog (3395), weighing 15 kilos. The fundus of the gall-bladder was stripped away from the liver and the cystic duct ligated.

TABLE E.

Substance.	Time (minutes).	Pressure (bile, mm.).
Before using drugs	25	60 to 65
Pilocarpin, gr. 1/12 (subcutaneously)	10	80 to 90
	12	80 to 90
	14	70 to 75
	8	50 to 55
Atropin, gr. 1/100 (subcutaneously)	17	65 to 70
	15	65 to 70
Adrenalin, 1 cc, 1 to 2600 (subcutaneously)	15	65 to 70

Discussion. It seems that the changes in the pressure within the gall-bladder due to the action of its musculature are very small. Qualitatively these results confirm the experiments of Lieb and McWhorter² who, using isolated strips of the gall-bladder wall, found that pilocarpin increased the tonus while atropin and adrenalin decreased it.

¹ New Orleans Med. and Surg. Sour., 1918, 71, 80.

² Jour. Pharm. and Exper. Therap., 1915, 7, 83.

Reciprocal or Contrary Innervation. In Experiments 3, 4, 5, 7 and 8, the effect of drugs acting either on the gall-bladder or the sphincter of Oddi was studied. Apparently, pilocarpin increases while atropin decreases the tonus of both. It seemed desirable to attempt a study of the simultaneous variations in the tonus of both gall-bladder and sphincter.

Experiment 9. May 18, 1923. Young male dog (3348), weighing 9 kilos; ether anesthesia. A cannula was placed in the common duct as in Experiment 3 and the duodenum opened. The fundus of the gall-bladder was stripped from the liver and the manometer was inserted as in Experiment 7. The cystic duct was carefully ligated avoiding the cystic artery. Pilocarpin and atropin were injected successively, and simultaneous observations on sphincter and gall-bladder tonus were made.

TABLE F.

Substance.	Time (minutes).	Pressure	
		Gall-bladder (bile, mm.).	Sphincter (saline, mm.).
Without drugs	20	25 to 30	110
Pilocarpin, gr. 1/12 (subcutaneously)	5	20 to 25	135
	7	25	115
	8	25 to 30	110
	10	30	120
	1	40	115
Atropin, gr. 1/100 (subcutaneously)	3	45	110
	5	10 to 15	105
	6	10 to 15	105
	8	20	110 to 120

Experiment 10. June 11, 1923. Young female dog (3384), weighing 8 kilos. Procedure as in preceding experiment. Magnesium sulphate applied in the duodenum over the papilla of Vater.

TABLE G.

Substance.	Time (minutes).	Pressure.	
		Gall-bladder (bile, mm.).	Sphincter (saline, mm.).
Without drugs	15	20 to 25	110
Magnesium sulphate (25 per cent)	2	20	100
	4	20	100
	10	20	90
	14	25	110

Experiment 11. May 16, 1923. Young male dog (3346), weighing 13 kilos; without anesthesia. Atropin gr. $\frac{1}{100}$ given subcutaneously; ten minutes later adrenalin (1 cc. of 1 to 2600) given subcutaneously. Under ether anesthesia, the abdominal cavity was opened at once. The gall-bladder was found normally distended with 15 cc. of dark viscid bile. The duodenum did not contain any bile similiar to that found in the gall-bladder.

Discussion. It may be concluded from these experiments that atropin decreases and pilocarpin increases simultaneously the tonus of both structures. Magnesium sulphate decreased the tonus of the sphincter without affecting the tonus of the gall-bladder.

In the qualitative experiment (Experiment 11) performed to study opposing innervation, after atropin (to relax the sphincter), adrenalin (theoretically to contract the gall-bladder?) did not effect an expulsion of the gall-bladder content.*

The Intra-abdominal Pressure. *Experiment 12.* Young male dog (3257), weighing 7 kilos, ether anesthesia. The cystic duct was ligated. A cannula was placed in the gall-bladder and a cannula in the common duct and both connected with calibrated upright manometers. The abdominal wall wound was closed tightly about them. The variation with respiration was observed in the column of bile. The depth and force of the respiration was altered by the degree of anesthesia and by pressure exerted manually on the abdomen or lower thorax.

TABLE H.

	Gall-bladder (bile, mm.).	Common duct. (bile, mm.).
Shallow respiration	40	3
Moderate respiration	80 to 100	6
Forced respiration	100 to 120	6

Experiment 13. Same animal as in Experiment 3 (3323). A piece of rubber tubing, in imitation of the common duct, was placed *in situ* and connected with a water manometer. The fluctuations observed were approximately the same as above.

Discussion. The above experiments demonstrate that there exists a large difference in the effect of the intra-abdominal pressure on the contents of the gall-bladder as compared with the effect on the contents of the common duct. In the latter the fluctuation produced by respiration is so slight as to be practically negligible. In the gall-bladder, however, an inspiration may cause a rise in pressure equivalent to three or four times the level which is normally maintained by the tonus of its wall. Furthermore, the pressure reached as a consequence of the respiratory squeeze is nearly twice that which was obtainable by extreme pharmacological stimulation such as the administration of pilocarpin (Experiments 7 and 8).

Summary of the Experimental Results. 1. The pressure in the common duct is relatively low, 60 to 65 mm. of bile, and varies but little.

2. Various agents (notably substances present in gastric chyme and magnesium sulphate) when placed on the papilla of Vater

* It is possible that there is an opposing innervation between the sphincter of Oddi and the pylorus. In a single experiment in which a small rubber balloon was placed in the pylorus, it was observed that adrenalin raised the pressure in the pyloric ring.

lessen somewhat the tonus of the sphincter of Oddi but usually not more than one-fifth to one-sixth of the original figure.

3. Of the drugs acting on the vegetative nervous system, atropin decreases and pilocarpin increases the tonus of both the gall-bladder and the sphincter of Oddi. Adrenalin decreases the tonus of the sphincter.

4. The musculature of the gall-bladder displays tonus variations but seems to possess little contractile power.

5. Contrary or reciprocal innervation or action between the gall-bladder and the sphincter of Oddi could not be demonstrated.

6. Increased intra-abdominal pressure, chiefly due to the inspiratory phase of respiration, effects a large pressure variation within the gall-bladder and almost none in the common duct.

BONE MARROW AND SPLEEN IN THE TREATMENT OF ANEMIA.*

BY CHAUNCEY D. LEAKE, PH.D.,

AND

JOSEPH S. EVANS, M.D.,

MADISON, WIS.

(From the Departments of Pharmacology and Clinical Medicine of the University of Wisconsin Medical School.)

A CONSIDERATION of the unsatisfactory results so often encountered in the traditional symptomatic treatment of various types of anemia by means of iron and arsenic led to a search for a more certain and reliable method of stimulating blood production. It has been shown by Whipple and his associates,¹ in a series of carefully controlled experiments, that neither iron nor arsenic exerts any significant effect on the curve of hemoglobin regeneration following simple anemia. In the opinion of these authors, diet is the most important factor in promoting hematopoiesis. Partial confirmation of this work was published by Musser,² who found that iron was of no value in stimulating blood formation in hemorrhagic anemia.

With detailed reports on their experimental studies, Hammett and his co-workers³ have advanced claims for germanium dioxide

* We desire to thank the following members of the staff of the Medical School for their hearty coöperation with us in the treatment of cases: Dr. W. S. Middleton, Dr. H. K. Tenney, Jr., Dr. R. C. Blankinship, Dr. R. R. Van Valzah, and Dr. H. M. Kay. We wish also to acknowledge our indebtedness to the careful technical work of Miss E. Kandell and Miss E. Thewlis.

A preliminary notice of this report was published in the Wisconsin Medical Journal in December, 1923.

as an efficient erythropoietic agent. Kast, Croll, and Schmitz⁴ found this substance satisfactory in clinical practice, and Lenker⁵ became enthusiastic over its effects in secondary anemia. Alexander,⁶ however, noted that it was inferior to arsenic and iron in pernicious anemia, while Minot and Sampson,⁷ as a result of their carefully conducted studies, could find no improvement in any type of anemic condition in which it was used. Further critical experimental investigation of germanium dioxide in animals by Bailey, Davidson and Bunting⁸ has shown that the early reports on its erythropoietic action cannot be substantiated. Although careful experimentation cannot as readily dispose of iron and arsenic as hematopoietic agents in the face of their long and successful clinical use as such, one is fully justified in seeking a more efficient and rapid means of promoting hematopoiesis.

As a way of approach to the problem, the following line of reasoning was tentatively adopted, which may be quoted from a previous publication:⁹

“(a) The production of red blood cells is not constant and maximum for existing red bone marrow, but, more in accordance with the general economy of nature, is regulated by the rate or extent of erythrocyte destruction, and a margin of reserve remains for the functioning of existing red bone marrow, with extension of the erythrogenic centers occurring only when this margin of reserve is exhausted under conditions of extraordinary stress; (b) the spleen, usually accepted as the organ chiefly concerned with the removal of the older erythrocytes from the circulation, elaborates, in proportion to the number of red blood cells removed, and possibly from them, a hormone capable of stimulating erythrocyte production; (c) this splenic hormone, being carried by the blood, lodges in the erythrogenic centers of the red bone marrow, either by means of an affinity of its own for them, or through the agency of a receptive substance in them capable of binding it, and (d) under the influence of this combination, and possible with the destruction of the hormone or hormones concerned in the process, the activity of the adult erythropoietic system is regulated.”

We are aware that various portions of this hypothesis conflict with the opinions of certain authorities,¹⁰ but it is compatible with the schema of the “hemolytopoietic system” as outlined by Krumbhaar,¹¹ and it was found to be convenient as a working theory.

Preliminary experimentation on dogs and rabbits, with adequate control studies, showed that splenic and red bone marrow extracts were powerful erythropoietic agents, and that they were more effective in combination than when used separately.⁹ The experiments indicated that these preparations acted first by increasing the rate of production or delivery in existing erythrogenic centers, and secondly by causing an extension of functioning red marrow.

Further experimentation on normal humans¹² confirmed these results and led to the belief that these materials when used in combination might prove helpful in certain types of anemia. It was shown that desiccated preparations were effective, and that they could be administered in capsule form. Not only was a marked rise noted in the number of circulating red blood cells (amounting to over 15 per cent in the case of the combined materials), but the hemoglobin content was also found to be considerably increased. Although this rise in the hemoglobin was not as rapid nor as great as the erythrocytic increase, it was better maintained when administration was stopped. Since the percentage of reticulocytes was much higher under the influence of the combined desiccated marrow and spleen, increased bone marrow activity was indicated. The increase in the number of reticulocytes, however, was not sufficient to account for the increase in red blood cells, so that some other factor, possibly augmented resistance to hemolytic processes, must have been involved. It was also noted that the absolute number of polymorphonuclear neutrophils was raised, that the blood volume did not change, and that there were not untoward accessory actions.

It has been pointed out¹³ that there is no compelling logic in the argument that because certain cells are formed in a special tissue, the latter must abound in available chemical stimulants for the productive activity in question. Furthermore, in view of this consideration, critical therapeutists have looked with doubtful approval on the proposals to use preparations of spleen and bone marrow as blood stimulants in anemia. It was stated that experience with numerous failures of vaunted hematopoietic agents warns against undue early enthusiasm when some new findings is announced. We have felt fully the force of these declarations and hence have subjected the experimental results to most careful scrutiny before undertaking clinical work. It is hardly necessary to indicate that the experimental studies only indirectly lend support to the hypothesis from which we started.

As has been inferred, many proposals have been made to use preparations of bone marrow and spleen for hematopoiesis in anemia. None of these, so far as we know, were based upon critical experimental work. Many scattered reports have appeared on the empirical use of such preparations in anemic conditions, and it may be of interest briefly to review the more important of these.

Red Bone Marrow. The use of red bone marrow in the treatment of anemia is nothing new. Osler and McCrae¹⁴ pointed out that it has the merit of a recommendation by Galen, and, indeed, during the last decade of the nineteenth century it came into widespread clinical use, only gradually to be discarded as newer methods of treating anemia gained prominence, and as new technic was introduced in the administration of iron and arsenic.

During this period, aside from an isolated experimental statement by Danilewsky and Selensky,¹⁵ the use of red bone marrow in the treatment of pernicious and secondary anemias rested almost entirely upon an empirical basis. According to Quine,¹⁶ Brown-Sequard and D'Arsonval in 1891 first suggested it as a remedy in conditions of defective hemogenesis. The first clinical paper on its effects appeared in 1892, by Kast and Rumpel,¹⁷ who used it in pernicious anemia. Within the next few years a considerable number of reports were made, in which red bone marrow was described as a valuable agent in effecting an improvement in various types of anemias. Usually saline extracts of freshly obtained red marrow was used, although in some cases glycerin extracts were said to be superior. Oral administration was invariably followed.

Four cases of chlorosis and secondary anemia successfully treated with fresh beef marrow saline extract were reported by Mann.¹⁸ Impetus to its use was given by the Edinburgh pharmacologist Fraser,¹⁹ when he presented a case of pernicious anemia greatly improved after a prolonged course of marrow treatment supplemented with iron, arsenic and salol. Billings²⁰ made an excellent study of its effects in 2 typical chloro-anemia cases, and in 2 patients suffering from grave pernicious anemia. He favored its use in chlorosis as a result of the great improvement in his 2 cases, in which the erythrocytes increased by a million cells within a month, and in which the hemoglobin percentage rose markedly, but not in proportion to the increase in red cells. In the cases of pernicious anemia, however, he noted an initial rise in erythrocytes and hemoglobin, followed by a gradual decline, and he cautioned against its use in this condition, pointing out that claims for improvement following the administration of red marrow in pernicious anemia must be carefully weighed in view of the difficulty of accurate diagnosis. An instance of this character was Danforth's report²¹ of the cure, by marrow and arsenic, of a case of apparent pernicious anemia, which eventually was shown to be malaria, and which ended fatally. Hamilton's paper,²² in which announcement was made of the prompt cure of 21 cases of severe anemia by glycerin bone-marrow extract can only be construed as an enthusiastic exaggeration. A report was made by Aleksieyeff,²³ however, that bone marrow was an excellent blood-producing agent in various chronic and wasting diseases. Barrs²⁴ had 1 case of pernicious anemia in which red bone marrow gave great improvement after arsenic had done no good, even though it had been pushed to the point of manifesting symptoms. In another instance, however, marrow alone resulted in no betterment. Drummond²⁵ found some gain under marrow in pernicious anemia, but it was much more marked when supplemented with arsenic. Contrary to most findings, Stockman²⁶ noted that both the erythrocytes and the hemoglobin fell under marrow treatment in pernicious anemia. In an excellent

review of the situation, Hunt²⁷ presented 3 cases of pernicious anemia, in whom red bone-marrow treatment resulted in slight improvements in the blood picture, which compared unfavorably, however, with the more striking betterment observed under arsenic. Hunt questioned the rationality of the treatment, doubting that the marrow extract supplied a deficiency, since this would be unlikely in pernicious anemia with an hypertrophied marrow. Hunt intimated that it served as a stimulant to an already overstimulated marrow. One of the last notices of the therapeutic use of red bone marrow in anemia was Brunton's²⁸ in which he described a marked improvement in a case of pernicious anemia treated with marrow tablets.

It may be of interest to note that a commercial preparation of red bone marrow—a glycerin extract of the material containing 2 per cent protein, 0.1 lecithin, 85 per cent glycerin, and undetermined iron—was admitted to New and Non-official Remedies in 1909,²⁹ but was subsequently removed.

Spleen. In contrast to red bone marrow, the therapeutic use of splenic extract has received but little attention from clinicians, to judge from the reports made, but the relation of the spleen to blood formation has been the subject of a great amount of experimentation and controversy. Not only has this study been direct in following blood changes after spleen administration, as exemplified by the reports of Danilewsky and Selensky,¹⁵ Goldscheider and Jacob,³⁰ Simon and Spillman,³¹ Brinchman,³² and Downs and Eddy,³³ but most intensive investigation has been made of the problem indirectly, by a study of the effects of splenectomy on the blood picture. Most independent workers on the matter—Zesas,³⁴ Pugliesse,³⁵ Wolferth,³⁶ Orr,³⁷ and Hitzrot,³⁸—agree more or less with the collaborated work of Austin, Krumbhaar, Musser, Pearce, and Pepper,³⁹ that splenectomy in normal animals results in (a) a slight to moderate anemia lasting from four to twelve weeks; (b) a leukocytosis which gradually declines; (c) an increased resistance of the erythrocytes to hypotonic saline. Since the anemia following splenectomy is accompanied with a diminution in the number of reticulo-cytes, Krumbhaar and Musser,⁴⁰ believe that the postsplenectomy anemia results chiefly from lessened blood formation, due to the loss with the spleen of a substance which normally stimulates the red bone marrow. This position is opposed by Paton and Goodall,⁴¹ Freytag,⁴² Asher,⁴³ and Gilbert,⁴⁴ but it is in accord with the fact that the administration of splenic extract in normal animals is followed eventually by an increase in the red blood cells, as found by Danilewsky and Selensky,¹⁵ Simon and Spillman,³¹ Eddy,⁴⁵ and as reported previously.^{9, 12} No explanation can be made of the leukocytosis following splenectomy,⁴⁶ but the increased resistance of the erythrocytes to hypotonic saline after this operation agrees with the observations of Bolt and Heeres⁴⁷ that the osmotic resist-

ance of the red blood cells is decreased by the spleen, while their resistance against saponin is increased by passage through this organ.

From a clinical point of view the reports of Carpenter⁴⁸ are of interest. He found splenic extract of value in treating typhoid fever and malaria. While he gives no figures, he states that the substance aids by increasing the number of leukocytes. A most interesting comment is made by this author to the effect that if the splenic extract does not produce the desired improvement, it should be combined with red bone marrow. The marrow extract seemed to activate the splenic extract in cases which did not respond to splenic extract alone.

Clinical. We wish clearly to emphasize that any attempt to promote hematopoieses in anemic conditions is, in general, only symptomatic treatment. No anemia can be considered cured unless the cause for it is determined and eliminated. If the attempt to improve hematopoiesis is successful, the effects of the anemia may be more or less alleviated, but the excessive strain on the blood-producing organs is present, and this cannot be regarded as a healthy situation. The restoration of blood function to normal, however, even if only temporary, may make it possible to attack more successfully the fundamental cause of the anemia by other methods. We hold, then, that the promotion of hematopoiesis in anemia is merely adjunctive to treatment directed toward the discovery and removal of the underlying cause of the condition.

In evaluating the results of any effort to stimulate erythrocyte and hemoglobin formation in anemic conditions many factors must be considered. As pointed out by Billings,²⁰ one must constantly keep in mind the difficulties of accurate diagnosis, of accurate estimation of the rate or extent of blood destruction as compared with blood regeneration and of estimating the capacity of an individual to regenerate blood. Moreover, the chronicity of the anemic condition and changes in the metabolic functions of the patient during the course of treatment greatly modify the objective criteria which should be used as a basis of judgment. One must seek rigorously to exclude the possibility of spontaneous improvement under the influence of factors not related to the treatment employed. Only long experience and a large series of carefully kept records, hard to obtain in ambulatory cases, can overcome the difficulty of comparing accurately the treatment in question with other forms of treatment in the same individual or in different patients. Finally, to emphasize the obvious, it is necessary to use the same instruments and technic throughout, and to maintain adequate control over the factors modifying blood concentration and distribution, and over whatever else may influence the blood picture.

In our clinical work on the symptomatic treatment of anemia by desiccated red bone marrow and spleen, we have followed 102 cases. Of this number, 65 are included in the present report as being satis-

factory with regard to the various factors mentioned above. The omission of 37 cases from this report does not in any way hide our failures since all these 37 patients showed improvement during the course of the treatment. They are not considered satisfactory for inclusion here because the possibility of spontaneous remission unrelated to the treatment cannot be excluded from 12, while in 4 the treatment was complicated by the use of other methods, and in the remaining 21, although improvement was noted in the records obtained, the data are not satisfactory because of failure on the part of the patients to return for final examination or for other reasons. All our unsuccessful cases are therefore included in those here reported although in 2 of these a case of anemia secondary to malignant endocarditis and one secondary to chronic tuberculosis, the records are far from satisfactory.

The desiccated spleen and red bone marrow powders, obtained through the courtesy of the Wilson Laboratories, were combined in equal proportions by weight, and were administered in 0.3 gm. (5 gr.) capsules, three times daily, before meals, with plenty of water. With improvement of the blood picture this dosage was diminished at first to 2 capsules and then to 1 capsule daily, the administration being withdrawn as soon as the erythrocyte and hemoglobin content of the blood remained constant.

TABLE I.—SUMMARY OF CASES.

Diagnosis.	Number of cases.	Markedly improved.	Moderately improved.	Slightly improved.	Not improved.
Pernicious anemia	2	2
Secondary anemia, cause unknown	15	4	8	3	..
Secondary anemia, cause known	48	13	22	8	5
Total	65	17	30	11	7

As may be seen from Table I, we have divided our 65 cases into 3 classes on the basis of diagnosis: (1) Primary progressive pernicious anemia, in whom not only were all the classical symptoms present, but in whom the disease ran a rapidly fatal course, with evidence of marked marrow injury, and without indicating an ability to regenerate normal blood; (2) secondary anemia without known cause, in whom the blood picture and symptoms varied from those usually associated with grave primary anemias to those generally considered indicative of mild chloro-anemia, but in whom the condition was more or less chronic, without a rapidly developing downward course, and in whom there was evidence of a substantial ability for normal blood regeneration; and (3) secondary anemia with known cause, in whom the blood picture and symptoms varied markedly, but which were usually those associated with chloro-anemia, and which seemed to depend greatly upon the gravity of

the underlying cause. We included 2 cases of what clinically appeared to be true chlorosis in this group, because, although the real cause is not clearly understood, it is certainly associated with faulty iron metabolism.

Clinically one sees wide variations in the blood picture and symptoms of the anemic individual. At times one may find a decrease due to such determinable causes as acute nasal infections, or digestive disturbances, but in some cases the cause cannot be determined. On the other hand, remissions may occur due to relief from the underlying cause, which may be spontaneous or due to remedial measures. This is especially true in those individuals with a cell and hemoglobin count around the lowest level of what may be considered normal values. A spontaneous remission occurring during treatment may therefore be mistaken for a real improvement due to the therapeutic agent. It was possible, however, to follow 10 of our cases over a period of two years, on the average, with careful clinical records before treatment with desiccated spleen and marrow was instituted. During this period these patients received many kinds of treatment, including administrations of iron and arsenic by various routes, without any significant or rapid change in the general level of their hemoglobin and cell count. We feel, since this level in these cases rose markedly upon the administration of desiccated spleen and marrow, and since the general improvement has been maintained, that we are justified in believing the change to be due to the treatment employed. The only comparison between desiccated marrow and spleen on the one hand, and iron and arsenic on the other, as hematopoietic agents, that we have felt it fair to make is in these same 10 cases.

In accurate hemoglobin and blood-cell determinations, the clinician has objective criteria for the study of anemia that are excellent in every respect if only the factors which may modify them are constantly kept in mind. In the majority of our cases the blood was drawn from both the finger tips and the ear lobes for simultaneous duplicate determinations. By this method, we believe we had a fair control on blood distribution insofar as local conditions in the capillary circulation were concerned. In 4 of our hospital cases we used blood which had been drawn from the median basilic vein for other purposes. Since the experimental work had indicated that marrow and spleen extracts do not have any significant effect on blood volume, we made no such determinations in the clinical cases, but rather insisted that our patients receive a large fluid intake. Blood was drawn from the patients in all cases at approximately the same hour of the day.

The duplicate blood-cell determinations were made with American standard hemocytometers and Levy counting chambers certified by the Bureau of Standards, while the hemoglobin determinations were made in duplicate using the Fleishel-Miescher hemometer, or Dare's hemoglobinometer.

In reporting the progress of our cases, we have used objective criteria only. Reliance was placed chiefly on the blood picture. If the hemoglobin percentage did not improve by five points, nor the erythrocyte count by 250,000 cells, the case was classified as showing "no improvement." An increase in the hemoglobin percentage between five and ten points, and in the red blood cell count between 250,000 and 500,000 cells, placed the case in the "slightly improved" class. If the hemoglobin percentage rose from ten to fifteen points, and the erythrocyte count from 500,000 to 1,000,000 cells, the case was noted as "moderately improved." An increase in a patient of over fifteen points in the hemoglobin percentage, and over 1,000,000 cells in the red cell count, was considered "markedly improved." Objective symptomatic criteria, such as dyspnea, cardiac thrills, edema, pallor, paraesthesia, and the like, noted especially in the more severe cases, were relieved in all patients as the blood picture improved. We have, furthermore, included in our cases which showed improvement only those in whom it was maintained or bettered as long as the administration of the desiccated spleen and marrow was continued.

We had 2 cases in which postmortem findings confirmed the diagnosis of primary progressive pernicious anemia. Neither of these showed any improvement in the blood picture under the influence of treatment with desiccated spleen and marrow. In fact, it seemed that the stimulus given the blood forming organs by this preparation was detrimental, in that it led to more rapid exhaustion, since the temporary improvement in the hemoglobin and erythrocyte count was followed by a sudden drop. It is difficult to diagnose between essential anemia of the progressive pernicious type in which the blood forming organs seem definitely to be injured, and grave secondary anemia of unknown cause in which the blood making functions appear to be inhibited or unable to meet the demands upon them rather than permanently damaged. In the treatment with marrow and spleen of the progressive pernicious type there has been a drop in the blood picture after an initial rise, while in the grave secondary anemias no such drop has taken place. The type of reaction, therefore, has been considered of diagnostic value, the preparation being discontinued whenever it failed to produce a positive response.

It may be of interest briefly to present an abridged case history of one of these patients suffering from primary progressive pernicious anemia.

CASE REPORT. The patient, a man, aged fifty-six years, was admitted to the Bradley Memorial Hospital on March 12, 1923, complaining of weakness upon exertion, shortness of breath and swelling in the abdominal region. These symptoms with tingling of the extremities and intermittent attacks of diarrhea, had been

present more or less constantly for the past two years. Upon examination he showed all the characteristic symptoms of pernicious anemia, including stomatitis, dyspnea, ascites, paresthesia of the extremities, cardiac thrills, capillary pulse, lemon-yellow pallor, and characteristic blood picture. The patient refused transfusion because of religious scruples. Treatment with desiccated marrow and spleen was instituted on March 13, with dietary and general hygienic regulations. A table showing the changes in the blood picture as treatment was conducted as follows:

Date.	Erythrocytes.	Leukocytes.	Hemoglobin per cent.
March 12, 1923 . . .	930,000	6500	25
March 13, 1923 . . .	900,000	6600	25
March 14, 1923 . . .	1,350,000	6200	32
March 15, 1923 . . .	760,000	4400	23
March 16, 1923 . . .	870,000	4600	28
March 17, 1923 . . .	950,000	4200	30
March 18, 1923 . . .	1,300,000	7200	31
March 19, 1923 . . .	1,020,000	6800	28

Treatment with desiccated spleen and marrow was discontinued on March 19. The blood picture continued to fall. Intramuscular injections of arsenic and iron failed to give any improvement at all, and on April 3, the patient died. A postmortem examination by Dr. C. H. Bunting confirmed the diagnosis of primary progressive pernicious anemia.

The other case ran a more prolonged course, but presented essentially the same features insofar as the blood picture was concerned when under treatment with desiccated spleen and marrow.

Secondary anemias without known cause are rather frequently encountered. In some cases the condition is progressive and may become grave. Careful search in such cases may often reveal a hidden focus of infection, the removal of which will clear the situation. In other cases, however, the condition is chronic and holds a stationary course. In these patients a history of severe infection or disorder in years past may be elicited, and it may be supposed that the blood-forming organs have never recovered normal activity from the strain placed upon them during that crisis. In such patients the use of desiccated spleen and marrow has been found to bring about moderate to marked improvement, where long continued treatment with iron and arsenic had been without significant effect. Of the 15 cases of secondary anemia without known cause which we have included in this study, 5 were of the active progressive type, probably due to some hidden focus of infection. Of these 5 patients, 3 were slightly improved under the influence of desiccated marrow and spleen, and 2 were markedly improved. The remaining 10 of this general class were cases of long continued chronic anemia, the cause of which had probably disappeared years previously. Of these cases, 2 showed a marked improvement, and

8 a moderate improvement under treatment with marrow and spleen.

A greatly abridged case report of 1 of these patients, briefly presented, may be of interest:

The patient, a married woman, aged sixty-one years, first came under observation at the University Clinic in 1919. At that time she complained of shortness of breath and weakness upon exertion. Careful physical examination revealed nothing significant. Her blood picture at that time was 55 per cent hemoglobin, 3,136,000 erythrocytes, and 7300 leukocytes. Treatment by means of intramuscular injections of iron and arsenic was begun, and continued at intervals for three years, during which time her blood picture slowly improved until in June, 1922, it reached 65 per cent hemoglobin, 3,510,000 erythrocytes, and 7080 leukocytes. Irregular administrations of iron and arsenic were continued for over a year, the last being October 12, 1923. On October 19, 1923, her blood picture was 65 per cent hemoglobin, 3,390,000 erythrocytes, and 6400 leukocytes. On this date treatment with desiccated spleen and marrow was instituted, and the course of her blood picture may be seen in the following table:

Date.	Erythrocytes.	Leukocytes.	Hemoglobin per cent.
Oct. 19, 1923	3,390,000	6400	65
Nov. 9, 1923	4,408,000	8400	75
Nov. 26, 1923	4,300,000	8400	78
Dec. 12, 1923	4,200,000	8100	82

On December 12, 1923, the administration of desiccated spleen and marrow was reduced to one capsule daily. On January 10, 1924, the blood picture was 80 per cent hemoglobin, 4,680,000 erythrocytes, and 6000 leukocytes. Administration was discontinued, and on February 11, 1924 the blood picture was 80 per cent hemoglobin, 4,110,000 erythrocytes and 6700 leukocytes, since then the patient has not been seen.

In Table II may be found a summary of the cases of secondary anemia with known cause which we have included in this report. Marked improvements were most consistently noted in patients suffering from menorrhagic anemia, and in the dietary anemias of infants. Two of the cases of menorrhagic anemia had run a chronic course for many years without relief of the anemic symptoms by means of treatment with iron and arsenic or dietary regulation. These two cases showed marked improvement in the blood picture and in clinical symptoms when treatment with desiccated spleen and marrow was instituted.

Some of the most remarkable results obtained by us in this study were in cases of grave anemias secondary to acute pyogenic infections. The sharp arrest of the downward course of the blood picture, its consequent rapid improvement, and the general better-

TABLE II.—SUMMARY OF CASES OF SECONDARY ANEMIA WITH KNOWN CAUSE.

Diagnosis.	Number of cases.	Markedly improved.	Moderately improved.	Slightly improved.	Not improved.
Chronic arthritis	7	..	6	1	
Menorrhagic	10	3	4	3	
Chronic tuberculosis . . .	6	2	1	1	2
Dietary anemia of infants .	5	4	1		
Pyelitis	2	..	2		
Streptococcemia	2	2			
Chlorosis	2	1	1		
Severe Dental and Nasal infection	2	..	2		
Malignant endocarditis .	1	1
Chronic endocarditis; hemolytic jaundice	1	1
Lung abscess	1	..	1		
Subacute cholecystitis . .	1	..	1		
Chronic salpingitis . . .	1	..	1		
Multiple osteomyelitis . .	1	..	1		
Chronic valvulitis	1	..	1		
Chronic sinusitis	1	1			
Cheilitis exfoliativa . . .	1	1	
Chronic eczema	1	1	
Gastric carcinoma	1	1	
Postoperative menopause .	1	1
Total	48	13	22	8	5

ment in the condition of the patient upon the administration of marrow and spleen were striking. A brief presentation of a case in question follows:

A University medical student, aged twenty-three years, was admitted to the University Infirmary on March 8, 1923, complaining of a sore throat. Examination revealed nothing significant except a deeply congested and swollen uvula. The patient stated that he suffered more or less chronically with sore throat. He was placed in bed and symptomatic treatment of the throat was undertaken. Rapid improvement took place, and the patient was to be discharged on the morning of the 16th. At 5:00 A.M. the patient called and complained of weakness and rapid heart-rate. The pulse was 160, with systolic pressure of 110 and diastolic pressure 80. There was no cardiac enlargement. On March 18 there was definite cardiac enlargement, with a soft systolic murmur, and continuation of the foetal rhythm. The cervical lymph glands were tender and slightly enlarged. On March 23, with subsidence of the cardiac involvement, an inflammatory condition of the right ankle was noted. On March 23 a positive blood culture was obtained, the organism being *Streptococcus buccalis* (viridans). On March 25 pretibial edema was noted on the left leg, with tenderness in both legs below the knees. Roentgen-ray examination revealed nothing significant. On April 5 the right ankle was drained; a green producing streptococcus corresponding in its cultural char-

acteristics to *Streptococcus buccalis*, being isolated from the pus. By April 11 both knees were involved along with the ankles. Drainage was instituted but the patient was weak and reacted acutely to pain.

The course of the blood picture of this patient before symptomatic treatment with desiccated spleen and marrow was begun, follows:

Date.	Erythrocytes.	Leukocytes.	Hemoglobin per cent.
Mar. 17, 1923 . . .	3,910,000	34,000	84
May 9, 1923 . . .	2,860,000	24,200	63
May 11, 1923 . . .	2,610,000	17,400	60

Treatment was instituted on May 12, the patient having become very weak. The subsequent course of the blood picture with continued treatment follows:

Date.	Erythrocytes.	Leukocytes.	Hemoglobin per cent.
May 16, 1923 . . .	3,810,000	14,200	81
May 18, 1923 . . .	3,840,000	15,400	84
May 22, 1923 . . .	4,010,000	12,600	90
June 6, 1923 . . .	4,490,000	11,300	90

Treatment with marrow and spleen was discontinued on June 6. The blood culture was negative May 22, the patient felt much stronger and was up daily in a wheel chair. Rapid improvement continued, the drainage wounds healed satisfactorily, and the patient was discharged July 7, 1923, with a blood picture of 92 per cent hemoglobin, 4,990,000 erythrocytes, and 10,800 leukocytes.

Of course, the drainage was the main factor of this case. The very rapid improvement in the blood picture in four days, however, and the maintenance of that improvement during the period of continued drainage, with evidence of varying degrees of toxin absorption as shown by the persistence of a remittent and intermittent temperature curve, was most significant of direct stimulation of hematopoiesis by the therapeutic measures employed. This rapid increase in blood formation, we believe, was a factor in this young man's recovery from pyemia.

In a somewhat similar case of streptococcemia quite as pronounced an improvement was noted following the use of desiccated spleen and marrow at a time when the blood picture was steadily falling.

In the dietary anemias of infants, our results were encouraging. The combined materials were administered in these cases as filtered saline broths in amounts appropriate to the age of the child. In these cases the red cell count rose rapidly and immediately, while the hemoglobin increased more slowly. These infants were all less than one year of age. An illustrative case follows:

A male infant, aged five months, was brought to the University Clinic on May 19, 1923. He was pale, emaciated and underweight. He had been bottle-fed since birth on a diet inadequate for his needs. His blood picture was 53 per cent hemoglobin, 2,908,000 erythrocytes, and 6700 leukocytes. Treatment with spleen and marrow broth was begun at once and continued until June 1. By this time arrangements had been made for the adequate regulation of diet and for daily exposure to sunlight.

The course of his blood picture while under observation follows:

Date.	Erythrocytes.	Leukocytes.	Hemoglobin per cent.
May 19, 1923 . . .	2,908,000	6,720	53
May 23, 1923 . . .	4,460,000	9,600	60
June 1, 1923 . . .	4,510,000	11,200	65
June 4, 1923 . . .	4,208,000	10,000	62
July 8, 1923 . . .	4,810,000	9,400	76

Similar improvements were noted in the other cases.

In the rest of our secondary anemias with known cause it may be seen that only moderate improvement occurred in the long-standing chronic conditions, while in the cases of endocarditis, one malignant, and the other chronic with hemolytic jaundice, no improvement at all was noted.

Discussion. We feel that desiccated spleen and red bone marrow constitutes a valuable addition to the armamentarium of the physician in the symptomatic treatment of secondary anemia. It rests upon fair experimental evidence and upon sound, though as yet insufficient, clinical results. Careful critical investigation of its action is forthcoming from independent sources. From reports reaching us from those therapeutists whom we have asked to coöperate with us in testing its clinical value, our results have had a certain amount of confirmation.

The use of desiccated spleen and red bone marrow in the symptomatic treatment of secondary anemia presents many advantages over the more traditional use of iron and arsenic. It lacks the dangers of the toxicity of arsenic, and it avoids the gastro-enteric actions of iron. It is as effective by mouth as by other routes, and the pain, expense, and technical requirements of the intramuscular or hypodermic injections of iron and arsenic, methods preferred because of the surety of absorption, are avoided. Furthermore, it seems to be much more rapid in its influence upon the blood picture, and is certainly as effective. From the subjective symptoms of our patients, and from objective improvements noted, we believe that it has a general therapeutic value in anemia at least equal to that of iron and arsenic.

The possibility that desiccated spleen and marrow are effective in promoting hematopoiesis because of their iron and lecithin contents cannot be denied. This was considered the basis of their action by Danilewsky and Selensky,¹⁵ and later by the Council

on Pharmacy and Chemistry of the American Medical Association when a glycerin extract of red bone marrow was admitted to New and Non-official Remedies.²⁹ We have determined the iron content of the combined desiccated preparation to be between 2.5 and 3 mg. per gm., using the colorimetric method of Wong.⁴⁹ According to Sherman,⁵⁰ this would represent about one-tenth of the daily iron intake on an average diet. The lecithin content of the combined desiccated preparation is one-third of egg yolk on the average, or about 30 mg. per gm. Whether these small amounts of iron and lecithin can so profoundly alter the blood picture of normal or anemic humans is a matter of conjecture.

In the preparation of these materials, the spleen is freed from connective tissue and fat before desiccation and powdering. The marrow is obtained from the short ribs of calves, and is dried and powdered after being only partially separated from calcium and fat by gross mechanical means. The calcium content of the desiccated marrow is between 20 and 30 per cent.

We realize that the results of treatment by desiccated spleen and marrow in 65 cases of anemia is not enough to serve as the basis for decisive conclusions, but it is felt that the results are sufficiently encouraging to warrant further careful and critical trial of this method of promoting hematopoiesis in secondary anemia. It is hardly necessary to indicate that this mode of treatment in anemia does not in any manner encroach upon the field of usefulness of transfusion in an emergency or acutely grave condition.

Clinical and experimental observations indicate that the combined preparation of spleen and red bone marrow stimulates cell production, and possibly increases cell resistance. If this assumption is correct, then it is indicated whenever the blood-making function are inhibited or are below the requirements of normal conditions, or whenever there is excessive erythrocyte destruction as in acute or chronic infections.

Summary. A review of the partially successful empirical use of marrow and spleen as hematopoietic agents justified an experimental investigation of these materials, in which it was demonstrated in normal animals and humans that they were more efficient in promoting hematopoiesis in combination than separately.

Desiccated spleen and red bone marrow combined in equal proportions by weight and administered in 0.3 gm. (5 gr.) capsules, has been found beneficial in the symptomatic treatment of secondary anemia, and presents many advantages over iron and arsenic.

In this report, 65 cases of various types of anemia are presented, in which the action of desiccated spleen and marrow has been carefully followed. Of these 65 cases, 47 were moderately to markedly improved with respect to the blood picture and other objective criteria, while 18 showed slight or no improvement. Among these latter are 2 cases of progressive pernicious anemia, the only cases of this class studied by us.

Desiccated spleen and red bone marrow may afford a valuable addition to the armamentarium of the physician in the symptomatic treatment of secondary anemia, and may be of diagnostic value in the differential diagnosis between progressive pernicious anemia and grave secondary anemia. The results thus far seem sufficiently encouraging to warrant further careful and critical trial of this method of promoting hematopoiesis.

BIBLIOGRAPHY.

1. Whipple, G. H., Hooper, C. W., and Robscheit, F. S.: Blood Regeneration Following Simple Anemia, *Am. Jour. Physiol.*, 1920, **53**, 151, 167, 206, 236, 263. Whipple, G. H. and Robscheit, F. S.: Iron and Arsenic as Influencing Blood Regeneration Following Simple Anemia, *Arch. Int. Med.*, 1921, **27**, 591.
2. Musser, J. H. Jr.: The Influence of Inorganic Iron on the Regeneration of Blood after Hemorrhagic Anemia, *Arch. Int. Med.*, 1921, **28**, 638.
3. Hammett, F. S., Nowrey, J. E., Jr., and Muller, J. H.: Erythropoietic Action of Germanium Dioxide, *Jour. Exper. Med.*, 1922, **35**, 173. Muller, J. H., and Iszard, M. S.: Erythropoietic Action, Cumulative Effect and Elimination of Germanium Dioxide, *AM. JOUR. MED. SCI.*, 1922, **163**, 364. Hammett, F. S., and Nowrey, J. E. Jr.: Source of Erythrocythemia Produced by Germanium Dioxide in Albino Rat, *Jour. Exper. Med.*, 1922, **35**, 507. Nowrey, J. E., Jr.: Effect of Sodium Germanate Upon the Total Hemoglobin of the Albino Rat, *Bull. Johns Hopkins Hosp.*, 1922, **33**, 340. Muller, J. H., and Iszard, M. S.: The Effect of Germanium Dioxide Upon the Blood, *Jour. Metab. Res.*, 1923, **3**, 181.
4. Kast, L., Croll, H. M., and Schmitz, H. W.: Therapeutic Use of Germanium Dioxide in Anemia, *Jour. Lab. Clin. Med.*, 1923, **7**, 643.
5. Lenker, J. L.: Pernicious and Secondary Anemias Treated with Germanium Dioxide, *Penn. Med. Jour.*, 1922, **26**, 86.
6. Alexander, M. E.: Action of Germanium Dioxide in Pernicious Anemia, *AM. JOUR. MED. SCI.*, 1923, **166**, 256.
7. Minot, G. R., and Sampson, J. J.: Germanium Dioxide as a Remedy for Anemia, *Boston Med. Surg. Jour.*, 1923, **189**, 629.
8. Bailey, G. H., Davidson, P. B., and Bunting, C. H.: Personal communication to the authors.
9. Leake, C. D., and Leake, E. W.: Erythropoietic Action of Red Bone Marrow and Splenic Extracts, *Jour. Pharm. and Exper. Therap.*, 1923, **22**, 75.
10. Bunting, C. H.: The Regulation of the Red Blood Cell Supply, Contributions to Medical and Biological Research, dedicated to Sir William Osler, 1919, **2**, 824.
11. Krumbhaar, E. B.: The Hemolytotoxic System in Primary Anemias, *AM. JOUR. MED. SCI.*, 1923, **166**, 329.
12. Leake, C. D.: Hematopoietic Effects of Desiccated Red Bone Marrow and Spleen in Normal Humans, *Jour. Pharm. and Exper. Therap.*, 1923, **22**, 401.
13. Editorial: *Jour. Am. Med. Assn.*, March 8, 1924, **82**, 797.
14. Osler, Sir. W., and McCrae, T.: Principles and Practice of Medicine, New York and London, 1922, p. 733.
15. Danilewsky, B., and Selensky, M. Über die blutbildende Eigenschaft der Milz und des Knochenmarks, *Arch. f. d. ges. Physiol.*, 1895, **61**, 264.
16. Quine, W. E.: The Remedial Application of Bone Marrow, *Jour. Am. Med. Assn.*, May 23, 1896, **26**, 1012.
17. Kast, A., and Rumpel, T.: Knochenmark bei pernicioser Anämie, *Path. Anat. Tafel Hamb Staats-krank. Wandsbek.*, 1892, vol. 3.
18. Mann, J. D.: Extract of Bone Marrow in the Treatment of Anemia, *Lancet*, 1894, **1**, 599.
19. Fraser, T. R.: Bone Marrow in the Treatment of Pernicious Anemia, *Brit. Med. Jour.*, 1894, **1**, 1172.
20. Billings, J. S.: Therapeutic Use of Extract of Bone Marrow, *Bull. Johns Hopkins Hosp.*, 1894, **5**, 115.
21. Danforth, I. N.: The Clinical History of Pernicious Anemia, *Chi. Clin. Rev.*, 1895-96, **5**, 80.
22. Hamilton, A. McL.: The Use of Medullary Glycerides in Conditions Attended

by a Paucity of the Red Corpuscles and Hemoglobin, New York. Med. Jour., 1895, 61, 44.

23. Aleksieyeff, F. K.: Bone Marrow as a Blood Producing Agent in Various Wasting and Chronic Diseases, Vrach. St. Petersburg., 1895, 16, 1057, 1091. Abstract furnished by Surgeon-General's Library.

24. Barrs, A. G.: A Case of Pernicious Anemia in Which Arsenical Palsy Had Been Induced Treated by Bone Marrow, Brit. Med. Jour., 1895, 1, 358.

25. Drummond, W. B.: A Case of Pernicious Anemia Treated with Bone Marrow, Brit. Med. Jour., 1895, 1, 1085.

26. Stockman, R.: Remarks on the Nature and Treatment of Pernicious Anemia, Brit. Med. Jour., 1895, 1, 965, 1025, 1083.

27. Hunt, G. B.: On Some Points in Pernicious Anemia with Special Reference to Treatment with Bone Marrow, Lancet, 1896, 1, 282.

28. Brunton, J.: A Case of Pernicious Anemia Showing Marked Improvement Under Arsenic and Bone Marrow, Lancet, 1905, 1, 87.

29. New and Non-official Remedies: Red Bone Marrow Extract, Jour. Am Med. Assn., June 12, 1909, 52, 1929.

30. Goldscheider, A., and Jacob, P.: Über die Variationen der Leukocytose, Ztschr. f. klin. Med., 1894, 25, 373.

31. Simon, P., and Spillmann, L.: Resherches experimentales sur l'action des injections d'extrait de rate: Reactions du sang, Comp. rend. Soc. de biol., 1906, 60, 833.

32. Brinchman, A.: Changes in the Blood after Experimental Feeding with Spleen Tissue, Act. Med. Scand., 1920, 52, 689.

33. Downs, G. W., and Eddy, N. B.: Influence of Splenic Extract on Number of Corpuscles in Circulating Blood, Am. Jour. Physiol., 1920, 51, 279. Effects of Subcutaneous Injection of Splenic Extract, *ibid.*, 1922, 62, 242.

34. Zesas, D. G.: Über Exstirpation der Milz am Menschen und Thiere, Arch. f. klin. Chir., 1883, 28, 157.

35. Pugliesse, A.: Neuer Beitrag zur Physiologie der Milz: Das Eisen der Galle und des Blutes bei entmilzten Thieren, Biochem. Ztschr., 1913, 52, 423.

36. Wolfert, C. C.: Blood Changes in Albino Rats Following Splenectomy, Arch. Int. Med., 1917, 19, 105.

37. Orr, T. G.: Blood Picture Following Experimental Splenectomy, Jour. Lab. Clin. Med., 1917, 2, 895.

38. Hitzrot, J. M.: The Effects of Splenectomy on the Normal Individual in Certain Pathological Conditions, Ann. Surg., 1919, 67, 540.

39. Musser, J. H., Jr.: An Experimental Study of the Changes in the Blood Following Splenectomy, Arch. Int. Med., 1912, 9, 592. Krumbhaar, E. B., Musser, J. H., Jr., and Pearce, R. M.: The Relation of the Spleen to Blood Destruction and Regeneration and to Hemolytic Jaundice, Jour. Exper. Med., 1913, 18, 119. Musser, J. H., Jr., and Krumbhaar, E. B., *ibid.*, 1913, 18, 487. Krumbhaar, E. B., and Musser, J. H., Jr., *ibid.*, 1914, 20, 108. Pearce, R. M., Austin, J. H. and Pepper, O. H. P., *ibid.*, 1915, 22, 682.

40. Krumbhaar, E. B., and Musser, J. H., Jr.: Effect of Splenectomy on the Hematopoietic System of Macacus Rhesus, Arch. Int. Med., 1923, 31, 686.

41. Paton, D. N., and Goodall, A.: The Spleen in Relationship to the Processes of Hemolysis, Jour. Physiol., 1903, 29, 411.

42. Freytag, F.: Beziehungen der Milz zur Reinigung und Regeneration des Blutes, Arch. f. d. ges. Physiol., 1907, 120, 501.

43. Asher, L.: Die Function der Milz, Deutsch. med. Wehnschr., 1911, 37, 1252.

44. Gilbert, Q. O.: The Occurrence of Nuclear Changes in the Red Blood Corpuscles Following Splenectomy, Arch. Int. Med., 1915, 15, 140.

45. Eddy, N. B.: The Internal Secretion of the Spleen, Endocrinology, 1921, 5, 461.

46. Leake, C. D.: Leukocytic Reactions to Red Bone Marrow and Spleen Extracts, Jour. Pharm. and Exper. Therap., 1923, 22, 109.

47. Bolt, N. A., and Heeres, P. A.: The Influence of the Spleen on the Red Blood Cells, Nederland, Tijdschr. Geneesk., 1922, 66, 2259.

48. Carpenter, C. R.: Splenic Extract and the Splenic Function, Med. Rec., 1900, 57, 273. Therapeutic Action of Splenic Extract in Malarial Infections, *ibid.*, 1906, 70, 165.

49. Wong, S. Y.: Colorimetric Determination of Iron and Hemoglobin in Blood, Jour. Biol. Chem., 1923, 55, 421.

50. Sherman, H. C.: Iron in Food and Its Function in Nutrition, U. S. Dept. Agric. Bull. 1907, 185, 79.

**SPLENIC ANEMIA: REPORT OF A CASE IN A LATE STAGE
CURED BY SPLENECTOMY.***

BY EDMUND HORGAN, M.D., F.A.C.S.

IN COLLABORATION WITH

WILLIAM P. REEVES, M.D., F.A.C.S.

AND

WILLIAM EARL CLARK, M.D., F.A.C.P.

WASHINGTON, D. C.

THE spleen, found in almost all vertebrates, is one of the chief parts of the lymphatic system. In mammals the spleen is situated in the upper left abdomen; in some of the lower vertebrates it is found in other abdominal regions. In sharks the splenic tissue is found in a number of small masses within the abdomen.

Physiology. The normal physiology of the spleen, or its associated functions with other organs and tissues is not clearly understood, but we know that its function is not essential to maintain the life of the organism, as its removal does not cause death. It is a passively elastic and contractile organ, depending on the amount of blood passing through it. The blood supply is from the splenic artery and the volume of blood which passes into the spleen at the hilum from the several branches of the splenic artery is very great. From the blood which passes through it, toxic substances, bacteria, parasites and disintegrated red-blood cells are removed by the spleen. Phagocytic leukocytes may or may not destroy bacteria and parasites within the spleen. Disintegrated cells, pigment from erythrocytes and toxic substances are carried through the splenic and portal veins to the liver. Here they are further acted upon and eliminated. By a study of the pathological and physiological changes found in diseases of the spleen and the blood, the associated function of the spleen with the liver, bone marrow, and blood has been confirmed.

Regeneration of Blood Cells in the Spleen. The primitive red and white corpuscles are nucleated. In vertebrates below mammals, the nucleus in the erythrocytes is found throughout the life of the cell and the cell is biconvex. In mammals, the erythrocyte loses the nucleus during fetal life and the cell becomes biconcave, but nucleated erythrocytes may be seen under normal conditions in the marrow of bones, in the blood of the spleen and occasionally in the blood of the portal vein. The erythrocyte is a cell distinctively characteristic of craniata. In acranial vertebrates and in inverte-

* Presented before The Medical Society of the District of Columbia, May, 23, 1923.

brates all blood corpuscles are nucleated and the oxygen is carried by the hemoglobin within the blood serum. From the mesenchyme cells the hemohistoblasts develop and by their further structural differentiation they form the endothelial cells of the bloodvessels, the erythrocytes, leukocytes, blood platelets and lymphocytes. The part the reticulo-endothelial cells in the blood sinuses of the spleen play in the regeneration of the blood cells is not known, but in some of the diseases of the spleen many nucleated erythrocytes and myelocytes are found which is suggestive of active cellular regeneration within the spleen.

Historical Data. Splenic anemia is one of the diseases in which changes in the liver and blood accompanying splenomegalia have been studied. Gretsels, who was first to report a case of splenic anemia, described and published a case from the clinic of Professor Greisinger. Greisinger had recognized clinically splenic anemia, which up to his time had been included in a large group of splenomegalias of unknown etiology. Gretsels gives Greisinger credit for having used the term splenic anemia to distinguish it from other anemias with splenomegaly, which had hitherto been classified as pseudoleukemias. The next important publications are those of Banti who reported the clinical observations and autopsy studies of 3 cases, and made other contributions to the literature on the disease. The writings of Banti became well-known and splenic anemia is often called Banti's disease, but Banti gives to Gretsels the credit of describing, and to Greisinger the credit of recognizing and naming splenic anemia.

The original group called splenic anemia by Gretsels included what we now recognize as Gaucher's disease, hemolytic jaundice, von Jaksch's disease, tuberculosis of the spleen, luetic and malarial splenomegalias, and thrombophlebitis of the portal and splenic veins. These diseases have been eliminated from the original group because clinical and laboratory studies have proved them to be entities in themselves. The splenomegalias which we now classify as splenic anemias are characterized by an insidious onset; chronicity over a period of years, with crises; a gradual hypertrophy of the spleen, accompanied by a secondary anemia with leukopenia, and occasionally, during a crisis, intermittent fever with leukocytosis; a tendency to hemorrhage from the mucous membranes but mostly from the stomach; at times attacks of epigastric pain; increase in the size of the liver at the beginning of the disease but contraction later as cirrhosis develops; and, in the terminal stage of the disease, jaundice.

Etiology. When splenic anemia was described by Gretsels and later by Banti the term included a number of splenomegalias, the etiology of which was unknown. From time to time as clinical, pathological and etiological studies were made, certain splenomegalias with splenic anemia were removed from the original group,

and in our present group of splenic anemias no definite cause has been found. It is reasonable to presuppose this present group includes splenomegalies due to several different causes, and that we are now including several distinct clinical diseases or entities. By further studies, we may be able to determine the etiological factors of each, so as to differentiate the several varieties now included. Although the etiology is unknown, it is considered that the disease is primarily in the spleen. In some cases the history would suggest as the underlying cause, some metabolic derangement or faulty intestinal absorption, present since childhood. Banti and others considered it of infectious origin and the cause of those splenic anemias, in which the etiology has been determined, substantiates this view.

Malaria and some other fevers of infectious origin cause enlargement of the spleen during their course. This enlargement in some cases remains after the symptoms of the disease have disappeared. Any one of these infectious diseases which causes an enlarged spleen may be an etiological factor in splenic anemia. When the spleen is damaged and its function deranged, by an infectious disease, it may be susceptible to splenic anemia, whatever the cause may be.

Symptoms. Banti describes splenic anemia as "a disease characterized by a gradual progressive oligemia of unknown cause, which gives place to marked disturbance of all organic functions, to edema, hemorrhage, intermittent fever; followed almost always by death; accompanied by a conspicuous tumefaction of the spleen and very often of the liver, the tumefaction independent of any previous morbid state and not accompanied by leukemic change in the blood. Briefly, splenic anemia is a progressive idiopathic hypertrophy of the spleen and frequently of the liver, without leukemia." He divided the progress of the disease into three stages: (1) Gradual enlargement of the spleen with secondary anemia; (2) hypertrophy of the liver with diminution in the amount of urine; and (3) reduction in the size of the liver, and ascites.

In our present group we consider splenic anemia to be a disease of early adult life, which may have been present for a number of years, but owing to its insidious onset unrecognized until the prominent symptoms became manifest. It is a chronic disease, progressing over a period of years. Early in the disease the spleen begins to enlarge, the enlargement being huge in many instances. The hypertrophy is gradual. Accompanying the hypertrophy of the spleen there is a secondary anemia with leukopenia. The erythrocytes number about 2,000,000 to 3,000,000 per c.mm., the leukocytes about 4000 to 5000 and hemoglobin about 50 per cent. Following the hypertrophy of the spleen there is an increase and later a reduction in the size of the liver. With the increase in the size of the liver, the amount of urine is reduced, and as the liver contracts the diminution is even more marked and there is an accompanying ascites. In the course of the disease there are crises, during which there may

be epigastric pain and hemorrhage which may be slight, or enormous in amount and sufficient to cause death. Most of the bleeding is from the stomach, but it may be from other parts of the gastrointestinal tract, or from the nose, kidneys and bladder, or there may be purpura. During a crisis there is intermittent fever, with leukocytosis. Late in the disease there is jaundice, the degree of which is dependent upon the damage to the liver. Beginning with the enlargement of the liver there is a gradual reduction in the amount of urine, with a marked diminution toward the terminal stage. The urine is high-colored and contains albumin and numerous casts.

Treatment. The recognized treatment of splenic anemia today is the administration of iron, transfusion and splenectomy. The administration of iron, either by mouth or subcutaneously, is of great value when the hemoglobin is lowered by the destruction of the erythrocytes or hemorrhage. Transfusion is a recent form of treatment and is an adjunct to the surgical treatment. Splenectomy for splenic anemia has been performed since the publications of Gretscl and Banti stimulated interest in this disease. Splenectomy had been performed before this time, and some of the earliest recorded cases of splenectomy might have been on cases of splenic anemia. Surgery of the spleen dates back to the Sixteenth Century. Splenectomy has been accredited by some authors to Zaccarelli in 1549 and to Ferrerius in 1711, but for lack of sufficient data these instances have not been accepted as authoritative. The earliest authentically reported cases of splenectomy are those of Quittenbaum of Rostock, in 1829, Kuchler of Dermstadt in 1855, and Spencer Wells of London in 1866. In each instance the patient died within a few hours following operation. In 1867 Pean did a successful splenectomy, from which the patient recovered. Collier's table, reporting 29 cases of splenectomy, covering a period from 1549 to 1881, shows a mortality rate of 72.4 per cent. Vanvert's thesis of 1897 gives a mortality rate of 37.9 per cent, recording 274 cases with 104 deaths. Mortality has since been reduced in splenectomy by proper selection of cases and employment of modern surgical technic. Giffin in 1921, in a series of 71 splenectomies for splenic anemia, reported only 9 deaths, a mortality rate of 12.6 per cent. The most favorable cases for splenectomy are those in which the spleen is only slightly enlarged, where only a moderate degree of secondary anemia exists, and where there has been no marked damage to the liver and other tissues. However, splenectomy has been done late in the disease, with favorable results, in cases which at first appeared hopeless. Lewis and Sweetzer have each reported a case of splenic anemia in which splenectomy was done late in the disease, following which the patient recovered. Having recently had under observation a patient who presented the characteristic clinical picture of splenic anemia, and in whom the disease progressed

to the third stage, and who was successfully treated by transfusion and splenectomy, we think this of sufficient importance to report in detail.

Case History. No. 1126.—Mr. V. B., a real estate broker, single, aged twenty-six years, was seen in consultation by me on January 28, 1922. There was no family history of disease of the blood or spleen. The patient gave a history of having had "liver trouble" at the age of seven years; typhoid fever at the age of eight; colitis at the age of fifteen and again at the age of seventeen. The present illness began seventeen years ago and has progressed steadily. He has had frequent digestive upsets which were considered "bilious spells," and was always inclined to be languid and drowsy. He took calomel and salts at frequent intervals. His symptoms were attributed to malaria, though this was not definitely established, as there were no chills, fever, or sweats, nor was the plasmodium found in the blood. At the age of seventeen years an enlarged spleen was first observed and since that time there has been a slowly progressive enlargement which has been accompanied by a gradually increasing secondary anemia. When the patient was twenty years of age, he had a hemorrhage from the bladder. In December 1917, at the age of twenty-one, he had a hemorrhage by mouth and in this same month he successfully passed the physical examination under enlistment in the Navy. His weight upon entering the Navy was 162 pounds. While in service in February, 1919, a hemorrhage by mouth occurred. On July 31, 1919, he was discharged from the Navy, his weight at this time being 196 pounds. At that time there was a very yellow cast to the skin and he was dark about the eyes. November, 1920, at the age of twenty-four years, he vomited a large amount of blood and passed tarry stools. Following this hemorrhage, blood examination on November 24, 1920, showed erythrocytes 2,190,000, leukocytes 20,800, hemoglobin 28 per cent. One week after this hemorrhage a diagnosis of duodenal ulcer was made, for which he was operated upon, elsewhere, on November 30, 1920, a gastroenterostomy being made. An omentopexy was also made on account of abdominal ascites. After the patient was operated upon, he improved, and was apparently in good condition. July 15, 1921, the erythrocytes numbered 5,500,000, leukocytes 7000 and the hemoglobin 80 per cent. In August, 1921, he had two roentgen-ray treatments over the splenic area of five and seven minutes duration, four days apart. Following this the patient became apparently worse and seemed exceedingly weak. On August 16, 1921, the erythrocytes numbered 4,300,000, leukocytes 6100, hemoglobin 82 per cent. Beginning on October 4, 1921, and continuing until October 8th, he had 11 hemorrhages. He bled from the mouth and rectum very profusely. On November 29 and 30, 1921, he again bled from the mouth and rectum (Table I).

TABLE I. HEMORRHAGES.

Date.	Age at time of hemorrhage.	Number of hemorrhages.	Location.
1916 . . .	20	1	Bladder.
Dec.. 1917 . . .	21	1	Mouth.
Feb. 1919 . . .	23	1	Mouth.
Nov. 1920 . . .	24	1	Mouth and rectum (profuse).
Oct. 4, 1921 . . .	25	4	Mouth and rectum (profuse).
Oct. 5, 1921 . . .	25	3	Mouth and rectum (profuse).
Oct. 6, 1921 . . .	25	3	Mouth and rectum (profuse).
Oct. 8, 1921 . . .	25	1	Mouth and rectum (profuse).
Nov. 29, 1921 . . .	25	1	Mouth and rectum (profuse).
Nov. 30, 1921 . . .	25	1	Mouth and rectum (profuse).
Total . . .		17	

During the gastroenterostomy operation on November 30, 1920, 2 gallons of fluid were taken from the peritoneum, and during the splenectomy operation on February 6, 1922, about the same amount was removed. From January 25, 1921 to March 16, 1922, the abdomen was tapped 46 times on account of abdominal ascites, withdrawing in all a total of $125\frac{3}{8}$ gallons of ascitic fluid. With the amount removed at operation the total is $129\frac{3}{8}$ gallons (Table II).

TABLE II. ABDOMINAL TAPPINGS.

Date.	Amount.	Date.	Amount.
Jan. 25, 1921 . . .	12 qts.	July 19, 1921 . . .	$12\frac{3}{4}$ qts.
Feb. 8, 1921 . . .	13 "	July 27, 1921 . . .	13 "
Feb. 11, 1921 . . .	8 "	Aug. 3, 1921 . . .	$12\frac{3}{4}$ "
Feb. 15, 1921 . . .	9 "	Aug. 10, 1921 . . .	$12\frac{1}{2}$ "
Feb. 21, 1921 . . .	8 "	Aug. 17, 1921 . . .	$13\frac{1}{2}$ "
March 2, 1921 . . .	14 "	Aug. 24, 1921 . . .	$11\frac{1}{2}$ "
March 9, 1921 . . .	13 "	Sept. 1, 1921 . . .	12 "
March 19, 1921 . . .	14 "	Sept. 8, 1921 . . .	$12\frac{1}{4}$ "
March 26, 1921 . . .	13 "	Sept. 17, 1921 . . .	10 "
April 2, 1921 . . .	13 "	Sept. 26, 1921 . . .	$9\frac{1}{2}$ "
April 11, 1921 . . .	12 "	Oct. 14, 1921 . . .	$7\frac{3}{4}$ "
April 21, 1921 . . .	$12\frac{1}{2}$ "	Nov. 7, 1921 . . .	$6\frac{1}{2}$ "
May 1, 1921 . . .	$13\frac{1}{2}$ "	Nov. 22, 1921 . . .	$8\frac{1}{2}$ "
May 11, 1921 . . .	14 "	Dec. 6, 1921 . . .	7 "
May 19, 1921 . . .	$14\frac{1}{2}$ "	Dec. 20, 1921 . . .	$7\frac{1}{2}$ "
May 26, 1921 . . .	$14\frac{1}{2}$ "	Dec. 28, 1921 . . .	7 "
June 2, 1921 . . .	$13\frac{3}{4}$ "	Jan. 4, 1922 . . .	$6\frac{1}{2}$ "
June 9, 1921 . . .	$15\frac{1}{2}$ "	Jan. 12, 1922 . . .	5 "
June 16, 1921 . . .	$14\frac{1}{2}$ "	Jan. 21, 1922 . . .	$5\frac{3}{4}$ "
June 23, 1921 . . .	$16\frac{1}{2}$ "	Jan. 28, 1922 . . .	$6\frac{3}{4}$ "
June 30, 1921 . . .	16 "	Feb. 4, 1922 . . .	$6\frac{5}{8}$ "
July 1, 1921 . . .	$12\frac{1}{2}$ "	Feb. 17, 1922 . . .	$2\frac{1}{2}$ "
July 9, 1921 . . .	$12\frac{1}{4}$ "	March 16, 1922 . . .	$\frac{1}{4}$ "

Total Number of Tappings — 46.

Total Amount — $129\frac{3}{8}$ gallons — (loss at operation estimated).

At the consultation on January 28, 1922, a splenectomy was decided upon, fully realizing that the condition of the patient made him a poor surgical risk.

Operation, February 6, 1922. The abdomen was opened through a high left rectus incision and upon exploration a moderately enlarged spleen was encountered. It was firmly adherent to the diaphragm, omentum, colon and stomach. With considerable difficulty the adhesions were separated and the spleen delivered through the abdominal incision. The pedicle was clamped, divided and ligated, and the spleen removed. Large hot packs were used to control the oozing from the under surface of the diaphragm. There was a large amount of ascitic fluid in the peritoneum. Exploration of the abdomen was difficult on account of numerous firm adhesions. The cecum could not be separated from adhesions holding it firmly in the right iliac fossa, and the appendix could not be brought into the operative field. The gall-bladder could not be palpated or inspected. The liver was small, hard and nodular and had the characteristic roughness of cirrhosis. As the spleen was being removed, Dr. Neuman transfused the patient with 500 cc of citrated blood (Table III).

TABLE III. TRANSFUSIONS

Date.	Amount.	Method.	Donor.	Reaction.
Oct. 5, 1921 . . .	650 cc	Direct	Brother	None.
Oct. 28, 1921 . . .	450 cc	Direct	Brother	None.
Nov. 14, 1921 . . .	600 cc	Direct	Friend	Fever, four days.
Feb. 6, 1922 . . .	500 cc	Indirect (citrate)	Friend	None.

Pathological Report. Weight of spleen 790 gm; it measures 19.5 cm. in length and 13 cm. in width. The superior surface is covered with a thick yellowish fibrinous exudate which is rough and torn in many places. The under surface in the region of the hilum is a dark lavender color. The organ sectioned with resistance. On section the surface is a dark purplish color with numerous trabeculations and thickened bloodvessels. The capsule is thickened and measures 3 mm. The exudate on the capsule measures 0.5 cm. (Fig. 1).

Microscopical Examination. The capsule is markedly thickened and is made up of a dense fibrous tissue. Over the surface of the capsule there is a fibrinous exudate throughout which there are numerous small round cells. In all the fields studied there is a marked fibrosis and the trabeculae are thickened. Only an occasional Malpighian body can be found and these show replacement with fibrous tissue (Figs. 2, 3, 4).



FIG. 1—(Case 1126.) Photograph of the superior surface of spleen, showing a marked perisplenitis.

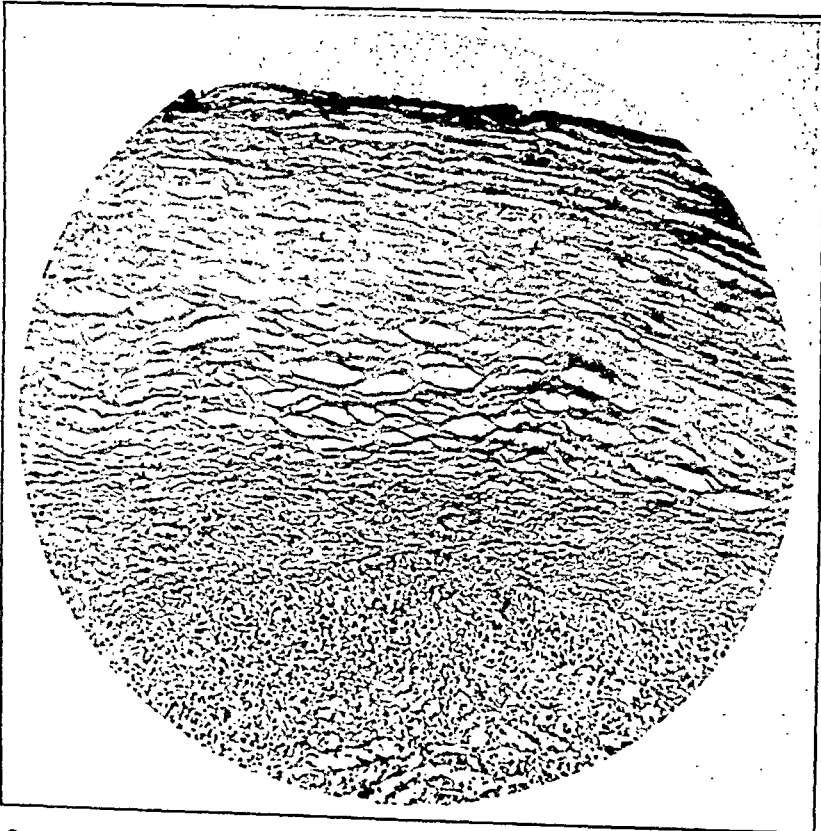


FIG. 2.—(Case 1126.) Photomicrograph of section of spleen, showing thickened capsule and fibrinous exudate on capsule. The exudate on capsule is made up of dense fibrous tissue, in which there is marked hyalinized fibrosis. The capsule is markedly thickened and is made up of a dense fibrous tissue, in which there is an infiltration of small round cells.

Pathological Diagnosis. Chronic splenitis.

Convalescence. For a few weeks after the operation there was a small amount of ascitic fluid in the abdomen, which soon ceased to accumulate. The convalescence was marked by bronchopneumonia, cystitis and separation of the wound. The bronchopneumonia and cystitis responded to treatment and the wound was resutured under local anesthesia. From this point convalescence was slow. The patient was weak and confined to his bed until the early part of April, when he was placed in a chair for a short time each day. After he was well enough to sit up, his appetite improved and an increase of strength was noted.

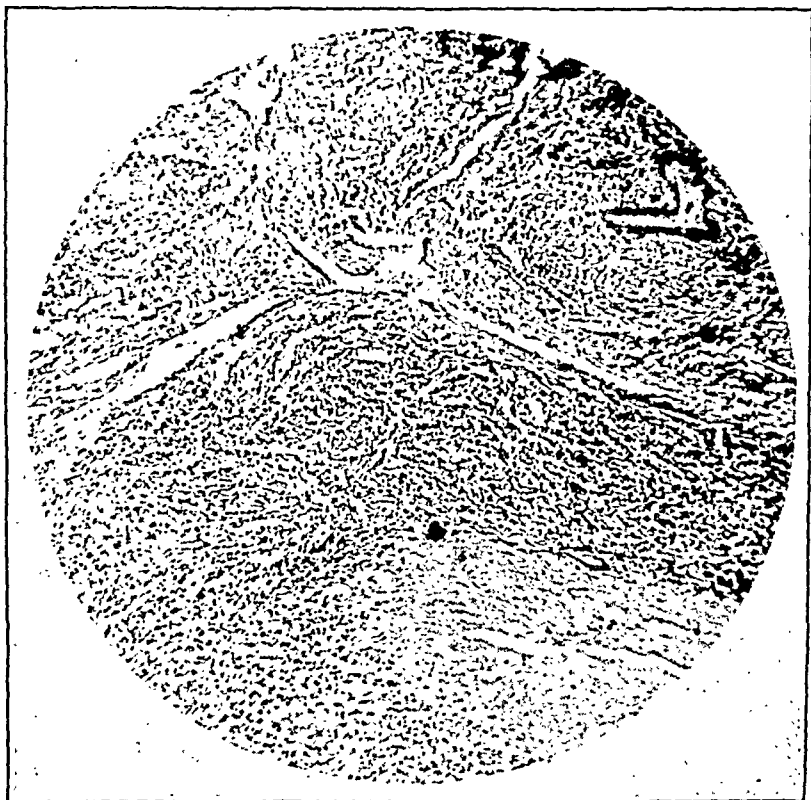


FIG. 3.—(Case 1126.) Photomicrograph of section of spleen, showing thickening of the trabeculae, marked increase in the fibrous tissue of the bloodvessels and fibrosis throughout the reticulum. The cells of the splenic pulp are made of lymphocytes, leukocytes and red blood cells, but are not numerous.

He continued to do well until the latter part of May, when he developed pain in the lower right quadrant of his abdomen, accompanied by tenderness and rigidity on pressure. There was a rise of temperature and nausea and vomiting. These symptoms became more marked and on June 2, 1922, a diagnosis of abdominal abscess was made, for which he was operated upon.

Operation, June 2, 1922. Under nitrous oxide-oxygen anesthesia, a split muscle incision over McBurney's point revealed a large

abdominal abscess, probably caused by an appendicitis, filling the lower right quadrant of the abdomen and the pelvis with thick pus. The abscess was evacuated of pus and drainage established. This abdominal abscess delayed convalescence considerably. It was not until about one month later that the patient could be gotten up in a chair again. After he was well enough to get up again his appetite improved, strength returned, and there was a gradual progressive improvement in his condition, so that by the end of the summer he was well enough to walk about a little.

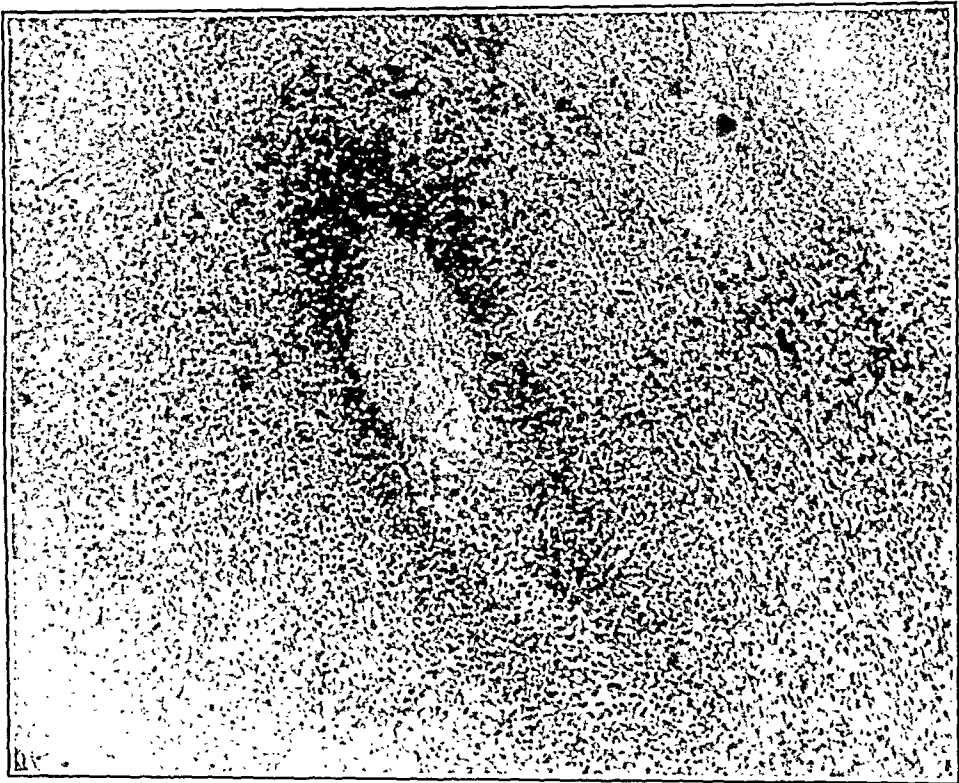


FIG. 4.—(Case 1126.) Photomicrograph of section of spleen, showing germ center, the central portion of which is made up of dense fibrous connective tissue which has contracted. There is a marked diminution of lymphoid cells.

On the evening of September 27, the patient became nauseated a few hours after supper and vomited. During the night an enema was given, but it was not very effective. The following day the nausea continued and the results of an enema were unsatisfactory. On September 29, 1922, the patient had fecal vomiting, the abdomen was distended, there had been no bowel movement, and a purgative enema, given at that time, was returned clear. A diagnosis of intestinal obstruction was made, for which immediate operation was advised.

Operation, September 29, 1922. The abdomen was opened through a low right rectus incision and exploration through it was made with some difficulty, on account of numerous adhesions. The

wall of the abdominal abscess, the upper part of which was formed by the terminal ileum, and omentum had contracted, producing several acute angulations of the ileum, which caused the obstruction. Part of the tissue forming the abscess wall was removed and the obstruction relieved by dissecting the ileum from its attachments. Following this operation the patient has continued to improve steadily. There has been a marked increase in strength, the weight gain has been over 80 pounds and his general condition is very good. On February 10, 1923, a cytological study of the blood showed erythrocytes 4,700,000, leukocytes 7000 and hemoglobin 90 per cent (Table IV).

TABLE IV. BLOOD COUNTS.

Date.	Hemoglobin.	Red blood corpuscles.	White blood corpuscles
Nov. 24, 1920	28	2,190,000	20,800
Nov. 25, 1920	33	2,240,000	
Nov. 26, 1920	32	2,320,000	
Nov. 27, 1920	31	2,190,000	
Nov. 28, 1920	35	2,310,000	
Nov. 29, 1920	38	2,620,000	
Feb. 1, 1921	55	3,500,000	5600
March 11, 1921	64	3,500,000	7600
June 15, 1921	80	5,550,000	7000
Aug. 16, 1921	82	4,300,000	6100
Oct. 1, 1921	68	4,536,000	7160
Oct. 4, 1921	60		
Oct. 24, 1921	33	1,784,000	8280
Nov. 13, 1921	33	2,896,000	8200
Nov. 18, 1921	75	3,430,000	7360
Nov. 25, 1921	60	3,000,000	5440
Dec. 7, 1921	55	2,550,000	7700
Jan. 16, 1922	31	3,370,000	5700
Jan. 24, 1922	50	2,980,000	4000
Feb. 6, 1922	Splenectomy		
Feb. 7, 1922	27,000
Aug. 21, 1922	75	3,500,000	9000
Feb. 10, 1923	90	4,700,000	7000

Conclusions. 1. Diseases of the spleen are uncommon and are often missed. In the case reported by Lewis and in this case, following vomiting of blood, a diagnosis of ulcer was made and a gastroenterostomy was done.

2. When a patient has a gastro-intestinal hemorrhage with epigastric pain, the spleen and blood should be studied.

3. The case of Lewis, that of Sweetzer, and the case reported here, demonstrate that a patient in a late stage of splenic anemia may be successfully splenectomized if he has had proper preparation by medical treatment and transfusion.

4. In the preoperative preparation, at the time of operation, and later, transfusion should be done as indicated.

5. Splenectomy should not be done in splenic anemia without considering the risk due to secondary anemia and damage to the liver and other tissues.

6. The recovery of this case helps to strengthen the view that whatever the cause of splenic anemia may be, it is primarily in the spleen.

BIBLIOGRAPHY.

Banti, G.: *Dell' Anemia Splenica*, Archivio della Scuola D'Anatomia Patologica, Firenze, 1883, 2, 53.

Collier, H.: Splenectomy: A Justifiable Operation in Leukocythemia (?), *Lancet*, 1882, 1, 219.

Ferreri: Quoted by Banti.

Giffin, H. Z.: The Present Status of Splenectomy as a Therapeutic Measure, *Minnesota Medicine*, 1921, 4, 132.

Gretsel: Ein Fall von Anemia Splenica bei einem Kinde, *Berl. klin. Wchnschr.*, May 14, 1866, p. 212.

Griesinger: Quoted by Banti.

Kuchler: Quoted by Banti.

Lewis, M. J.: Splenic Anemia, Splenectomy and Recovery, *AM. JOUR. MED. SCI.*, 1908, 136, 157.

Peau: Quoted by Banti.

Quittenbaum: Quoted by Banti.

Sweetzer, H. B.: Splenectomy in Third Stage, Banti's Disease, *Surg. Gynec. and Obst.*, 1921, 33, 376.

Vanverts, J.: Thèse pour le Doctorat en Medecine de la Splenectomie, 101, Paris Thesis, 1897.

Wells, Sir T. S.: On Excision of Enlarged Spleen with a Case in Which the Operation was Performed, *Med. Times and Gaz.*, 1866, 1, 2.

Zaccarelli: Quoted by Banti.

COMBINED SCLEROSIS OF THE SPINAL CORD AND CARCINOMA OF THE STOMACH.

REPORT OF A CASE.

BY JOHN L. GARVEY, M.D.,

AND

LOUIS D. STERN, M.D.,

ANN ARBOR, MICHIGAN.

(From the Departments of Neurology and Internal Medicine, University of Michigan Medical School.)

CASES of combined degeneration of the spinal cord associated with carcinoma of the stomach and simulating pernicious anemia are sufficiently rare in the literature to warrant reporting. Hurst, commenting on a case of this type reported by Waterfield and Shackle,¹ states that he and Bell² failed to discover any record of an actual case of cancer of the stomach with subacute combined degeneration of the cord. Several writers, however, have referred to the possible occurrence of such an association as an alternative

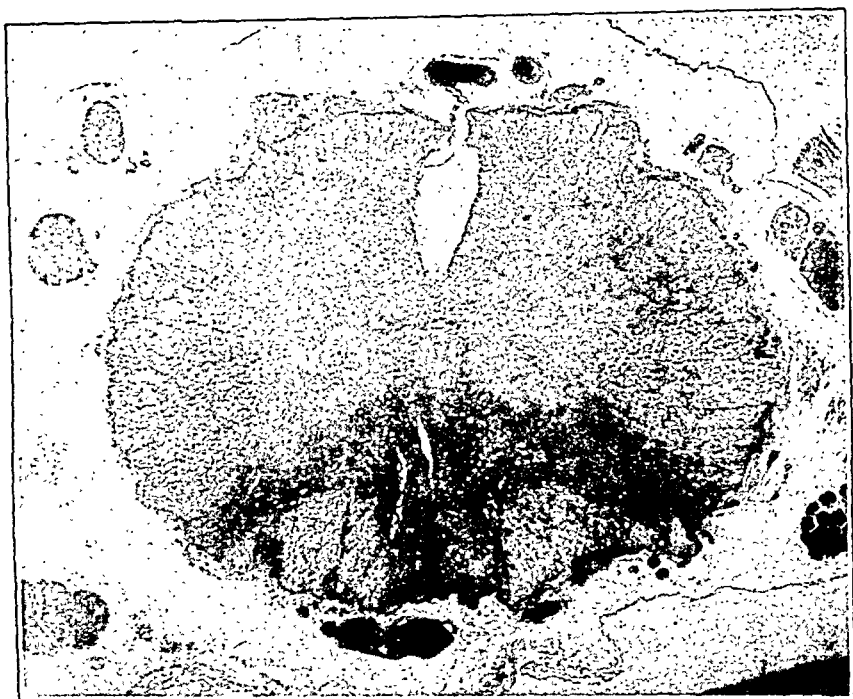
to the more common one in Addison's anemia. Hurst and Bell advance the opinion that the achlorhydria of pernicious anemia, with or without subacute combined degeneration of the cord, is not the result of any specific gastric disease, as it might ensue from a variety of causes; and there is no reason why cancer of the stomach should not be one of these.

Case Report. An adult male, aged fifty years and a janitor by occupation, entered the Clinic for Neurology of the University Hospital, November 21, 1922, complaining of numbness and tingling in the hands and feet. His father had died of cancer. He had never married, insisted he had had no previous serious illness and denied venereal disease. His present illness was of rather short duration. About a month previous to entrance he noticed that his hands and feet would become swollen following heavy work, and shortly after this he experienced numbness and tingling in the extremities. These symptoms progressed and he soon found that he could not ride a bicycle which he had been in the habit of doing. He had no other complaints referable to the gastrointestinal, cardiovascular or nervous system.

Examination showed that he was only fairly well nourished and he appeared about his actual age. He seemed mentally normal and of about average intelligence. There was a definite lemon-yellow color to the skin, and the sclerae were china blue. The tongue was smoothed out and tremulous. The pupillary reflexes were somewhat slow. There were no extraocular palsies and no nystagmus, and the function of the other cranial nerves was normal. He wore an upper plate and the few remaining teeth showed some caries. The right hand was somewhat puffy. The tendon reflexes were all present, prompt and equal. There was a marked spinal ataxia on the finger-to-nose test, and his gait was of the bilateral spastic ataxic type. Sense of motion and position was lost in the toes, and deep muscle sense was lost in the ankles. Vibratory sense was normal. The plantar reflex at this time was flexion. Both eyes showed early lenticular changes and the fundus was of the arteriosclerotic type. Examination of the heart, lungs and viscera of the abdominal cavity was entirely negative. Blood-pressure was 105/70. The urine examination was negative. The Wassermann test on the blood and spinal fluid was negative, and the spinal fluid was normal to other chemical and serological tests. Examination of the blood at this time showed hemoglobin 81 per cent, red blood cells 3,150,000, white blood cells 5100 with a normal differential white cell picture and no noteworthy changes in the red cells indicative of pernicious anemia.

In view of the association of a combined degeneration of the spinal cord, an anemia and a lemon-yellow color of the skin it seemed reasonable to assume that this was a syndrome of rather common occurrence. Woltman³ believes that this type of cord involvement

with an anemia which does not show the characteristics of the pernicious type is nevertheless potentially of that type; and the literature is quite full of reports of cases of posterolateral sclerosis which eventually develop the classical picture of pernicious anemia. Moreover, the case here presented did show one of the most characteristic blood findings of Addisonian anemia; namely, a high color index. The diagnosis of that disease therefore was strongly entertained.



Low-power photomicrograph of the spinal cord, from the authors' case, showing sclerosis of the type and distribution associated with pernicious anemia. (Courtesy of Professors Warthin and Weller.)

Repeated blood examinations over a period of several weeks with the expectation of showing some significant change, revealed no further evidence of primary blood disturbance, although the anemia progressed and the hemoglobin decreased to 60 per cent. Gastric analysis showed absence of free hydrochloric acid and very low total acidity. Examination of the stool was entirely negative.

After about six weeks in the hospital the patient began to complain of slight gastric disturbance after eating, not amounting to pain. He noted a feeling of fullness, which he attempted to relieve by induced emesis. The vomited material after a meal was excessively large in amount and contained numerous yeasts and Opple-Boas bacilli, no free hydrochloric acid, no blood. Gastrointestinal roentgen-ray at this time revealed a permanent prepyloric defect, typical of gastric carcinoma. In view of the evidence of pyloric obstruction, operation was advised and posterior gastroenterostomy

was done. The surgeon noted extensive carcinoma with lymph gland metastases, and incidentally an apparently normal spleen and liver.

Recovery from the operation was uneventful, and for a time there was relief from the gastric symptoms. About six weeks later, however, it was seen that the patient was losing weight with the return of vomiting and the onset of epigastric pain, which had not been present before. During the ensuing month he became progressively worse in every respect. The knee and ankle reflexes became exaggerated and later were entirely lost, with a complete paralysis of the lower extremities and retention of urine. On May 19, 1923, six months after admission to the hospital, he died.

Autopsy Findings. The spinal cord showed marked posterolateral degeneration of the type seen in pernicious anemia, more marked in the dorsal than in the cervical region. A diffusely infiltrating adenocarcinoma was found to involve the pyloric end of the stomach, with metastases in the peritoneum and mesenteric lymph nodes but with none in the cord or bone marrow. The bone marrow was hyperplastic. The liver and spleen showed only chronic passive congestion and atrophy, without malignant metastases and without any increased deposition of iron.

Discussion. The clinical and pathological findings definitely established the coexistence here of combined sclerosis of the spinal cord and carcinoma of the stomach. The question of primary interest concerns the possibility of an accompanying pernicious anemia of which the cord lesion may be a part. If, as has been argued by Woltman³ and others^{2, 4, 5}, the presence of combined sclerosis with an anemia of any type is sufficient for a diagnosis of pernicious anemia, then that disease is certainly not to be easily eliminated in this case. Carcinoma of the stomach has been noted in the presence of undoubted pernicious anemia⁶ although the signs and symptoms leading to such diagnoses are often to be explained on the basis of the cancer alone. For this reason much of the clinical data bearing on the question is useless. It is conceivable that the case under discussion would eventually have developed typical pernicious anemia had the cancer not killed him, but this involves the assumption that death was due primarily to the carcinoma which may not have been the case. Indeed, from the clinical standpoint, the signs of spinal cord degeneration progressed about as rapidly toward the termination of the case as did those of the cancer, and may have contributed just as much toward determining the outcome.

The most important single diagnostic feature of pernicious anemia is naturally the change in the blood, and one of the most characteristic details of this change is the high color index. This alone, among all the special features to be expected, was found in this case, and there was no marked fluctuation in the blood picture

at any time. In view of the well established fact that uncomplicated cancer of the stomach may produce this sign, no weight can be placed upon it as favoring the existence of a primary blood disturbance.

The sclerosing glossitis so commonly seen in pernicious anemia, which was noted in this case, is not necessarily indicative of that disease, for it may unquestionably be encountered under other conditions; and every case of true Addisonian anemia does not always show it. While it is an undoubted aid in diagnosis, there is no definite reason for considering it a specific sign of any greater value than the achlorhydria, to which it may be closely related. Just as the absence of free hydrochloric acid in the stomach may be due to a variety of causes, notably to cancer, so the glossitis may, under unusual conditions, be due to other agents. As an example of the occasionally misleading and unusual combination of signs, it may be stated that the writers have recently observed a case of disseminated sclerosis with achlorhydria, which came to autopsy, and in which the cord lesions were so distributed as to give rise to signs which simulated closely the typical findings of combined sclerosis.

The possible etiologic relationship of achlorhydria to combined sclerosis of the cord has been pointed out particularly by Hurst and Bell² and Vanderhoof.⁷ From this point of view it is possible to consider the foregoing case as one primarily of cancer of the stomach, with the cord lesions developing as a result of the deficient gastric secretion. The history of the case lends some color to this conception because the symptoms of the spinal cord degeneration were of relatively short duration, and antedated the onset of definite gastric disturbance by only ten weeks. Moreover, the progress of the case indicates that both the carcinoma and the posterolateral sclerosis developed rapidly and coincidentally, in such a way as to make it very difficult, if not impossible, to decide which pathological process contributed more toward determining the final outcome. This idea is purely theoretical, however, for combined sclerosis of the spinal cord has never been noted as a true complication of gastric cancer in any of the innumerable cases of that disease on record.

From the pathological standpoint, the presence or absence of true pernicious anemia in this case cannot be definitely determined. The hyperplastic bone marrow is suggestive, but far from conclusive. The hemosiderosis of various organs, particularly of the liver, spleen and kidneys, which has been stressed by the older writers as being so characteristic of pernicious anemia, is not an invariable finding at autopsy. Absence of it, therefore, does not eliminate the disease.

The question as to whether or not pernicious anemia was present in the foregoing case cannot be definitely answered. The diagnosis

may or may not be made according to the criteria of various competent observers. On the basis of the general diagnostic rule that signs and symptoms are to be explained by the simplest plausible diagnosis, it would seem that the presence of pernicious anemia is not necessary to explain the findings. While it is probably true that the majority of cases presenting a combined sclerosis of the spinal cord and an anemia will eventually show the changes found in pernicious anemia, it must nevertheless be borne in mind that this general rule will have its exceptions. In the diagnosis of any particular case, certain details of the examination may be found to assume unexpected importance and may materially alter not only the clinical interpretation, but the prognosis and treatment as well.

Summary. 1. A case of combined sclerosis of the spinal cord and carcinoma of the stomach, with autopsy findings, is reported.

2. The close resemblance clinically and pathologically between this combination of diseases and that including pernicious anemia is pointed out.

3. The importance prognostically and therapeutically of determining the etiology of an accompanying anemia in cases of combined degeneration of the spinal cord is emphasized.

REFERENCES.

1. Waterfield, R. L., and Shackle, J. W.: *Guy's Hospital Reports*, 1923, 73, 208.
2. Hurst, A. F., and Bell, J. R.: *Brain*, 1922, 45, 266.
3. Woltman, H. W.: *Collected Papers of the Mayo Clinic*, 1918, 10, 933.
4. Hurst, A. F.: *Brit. Med. Jour.*, 1924, 1, 93.
5. Bramwell, B.: *Brit. Med. Jour.*, 1910, 1, 1396.
6. Brandes, T.: *Med. Klinik*, 1921, 17, 189.
7. Vanderhoof, D.: *Arch. Int. Med.*, 1923, 32, 958.

THE TREATMENT OF TETANUS, WITH SPECIAL REFERENCE TO THE USE OF MAGNESIUM SULPHATE.

BY CARROLL SMITH, M.D., F.A.C.S.,

PROFESSOR OF SURGERY, ST. LOUIS UNIVERSITY, SCHOOL OF MEDICINE,

AND

W. E. LEIGHTON, M.D., F.A.C.S.,

PROFESSOR OF SURGERY, ST. LOUIS UNIVERSITY, SCHOOL OF MEDICINE,
ST. LOUIS, MO.

(From the Department of Surgery, St. Louis University, School of Medicine.)

WHILE great advances have been made in our knowledge of tetanus since the discovery of the "bacillus of earth," by Nicolaier¹ in 1884, and the isolation of the tetanus bacillus, by Kitasato² in 1889, and the introduction of tetanus antitoxin, by Behring and

Kitasato³ in 1890, nothing has been found which will overcome the strong combination between tetanus toxin and nerve tissue. We must admit that the treatment of tetanus still is prophylactic and symptomatic.

The prophylactic value of antitoxin in tetanus is so evident that any fair-minded man should be convinced, and it is not necessary to produce the numerous statistical reports and experimental evidences which prove this assertion. It is true that tetanus antitoxin does not always prevent the development of tetanus, but the prophylaxis is successful in the great majority of cases, when the serum is properly administered. Tetanus may develop after prophylactic serum according to Donati⁴ as follows:

1. Mild tetanus after a long incubation period.
2. Local or partial tetanus.
3. Fulminating tetanus, with a very short incubation period.

Kuemmell⁵ states that a small number of individuals are so very susceptible to tetanus toxin that the antitoxin fails to function. Tulloch⁶ points out that there are at least three different strains of toxic and more than one non-toxic strain of tetanus bacilli, and this may account for the failure of prophylactic antitoxin at times. To these types should be added late and recurrent tetanus. Ashhurst⁷ states that the prophylactic effects of the serum disappear between eight and ten days, so that dormant bacilli or spores may become active after that period, and produce typical symptoms. Speed⁸ has called attention to recurring tetanus, and reports a case recurring seventeen months after the original attack. Recurring tetanus after serum usually follows the retention of a foreign body. This was the condition in Speed's case and similar cases are reported by Stauff,⁹ Bungart¹⁰ and others. Vernoni¹¹ mentions 4 cases, apparently cured of tetanus, in which new attacks were aroused by trauma or operations. Montois¹² and Courtois-Suffit¹³ state that dormant spores may be awakened months after implantation. Kuemmell⁵ and Courtois-Suffit¹³ emphasize the importance of giving tetanus antitoxin just before operation, performed after a recent attack of tetanus or a recent suspicious wound. Courtois-Suffit¹³ and Gessner¹⁴ advise repetition of the prophylactic serum in seven to ten days in the presence of suppuration. Bruce⁵⁵ advises that the primary injection of prophylactic serum be followed by secondary and further prophylactic doses, as long as the wound remains suspicious.

While 1500 units of serum given at once, and repeated in ten days, generally is used, Ochsner¹⁵ advises ten times this dose. Chavasse¹⁶ states that the prophylactic dose of serum should be in proportion to the gravity of the wound, and that it should be increased especially in the presence of a foreign body.

It was found early that tetanus antitoxin would not cure tetanus after the symptoms were present, due to the firm combination of

the toxin with nerve tissue. It also was recognized early that sedatives were needed in the treatment, as it was realized that death was due to exhaustion, starvation or asphyxia during a spasm, and not directly to the toxin. Many sedatives have been advised, such as morphin, chloral, chloretone, by Hutchings;¹⁷ persulphate of soda by Bérard and Lumière;¹⁸ Du Bouchet,¹⁹ a preparation of curare called curaril; by Bergell and Levy,²⁰ spinal injections of morphin and eucaïn by Murphy;²¹ intravenous ether-salt solution by Hercher,²² and later luminal. All these preparations did not meet expectations.

In 1899 Meltzer²³ first noticed that the effect of magnesium salts was inhibitory when given intracerebrally in rabbits. In 1905 Meltzer and Auer²⁴ studied experimentally the effects of magnesium salts on numerous animals, and they found that the effect always was inhibitory and no stimulating action was ever seen. In later experiments they^{25, 26} studied the effects of magnesium salts when given intravenously, intramuscularly and intraspinally, and they found in each case that the effect always was inhibitory and tended to produce paralysis.

Meltzer and Auer²⁷ then studied the effects of magnesium sulphate in the treatment of tetanus in monkeys and found that it had marked influence in controlling the spasms in these animals. Acting on these findings of Meltzer and Auer, Blake²⁸ treated the first case of human tetanus in a boy by magnesium sulphate in 1906. He used intraspinal injections of magnesium sulphate and succeeded in curing a very severe case of tetanus. Other early, successful cases were reported by Logan,²⁹ Miller,³⁰ Hessert,³¹ Kocher,³² Robertson³³ and others.

There is no question that the use of magnesium sulphate is the greatest advance in years in the treatment of tetanus. The effect is purely symptomatic. It acts to prevent death from exhaustion or asphyxia, until the patient is able to eliminate the toxin which is in combination with nerve tissue. The effect comes on very soon after the injection. Under appropriate application the patient becomes quiet, the spasms become less, or disappear, and the spastic muscles relax. The patient takes nourishment, is comfortable and sleeps. Straub³⁴ noted that magnesium sulphate relaxed spastic muscles before affecting normal muscle function.

Magnesium sulphate may be administered by four routes: Subcutaneous, intramuscular, intravenous and intraspinal. A 25 per cent solution of chemically-pure crystalline magnesium sulphate should be used in all methods, except the intravenous, where a 6 per cent solution is employed. The solution should be sterilized by boiling, or in the autoclave.

Weston and Howard,⁵⁶ who recently have reported excellent results in using magnesium sulphate, subcutaneously and intramuscularly, as a sedative in patients suffering from psychic dis-

turbances, advise that crude magnesium sulphate should be recrystallized three times, in order to secure a pure product. In the *subcutaneous method* 1.2 to 2 cc of a 25 per cent solution to each 20 pounds of body weight should be used four times in twenty-four hours. In severe cases 16 cc of the solution should be used four times in a day. The treatment should be repeated until all symptoms have disappeared. By this route the action is slower, but it is cumulative. It is the least dangerous method, but it may not suffice in very severe spasms unless large doses are given. In *intramuscular administration* Meltzer³⁵ advised that the patient be anesthetized by ether, then 2 cc of a 25 per cent solution to each 20 pounds of body weight should be injected into the muscles. This method may bring relief in less than half an hour and the effect lasts for two or three hours. The drug is more toxic by this method, and it should not be employed as a routine measure, but withheld for severe spasms. The *intravenous method* gives a more prompt effect than any other method, but its action may disappear in thirty minutes. This is a dangerous method, as the myocardium may be affected if the drug is injected too rapidly and respiratory paralysis is then prone to occur. It should be used only in great emergency, such as spasm of the diaphragm or larynx, where quick action is demanded, and means, as mentioned below, for treating the serious effects should be at hand. By this method Meltzer³⁶ advises a 6 per cent solution of magnesium sulphate given at the rate of 2 to 3 cc per minute and stopped as soon as there is beginning relaxation, or when serious heart or respiratory symptoms appear. These untoward effects disappear rapidly after the injection is stopped. When used by the *intraspinal method* the effect usually is manifested in less than a half hour and complete relaxation is present within one hour. The relief is longest by this method and lasts from twelve to thirty hours. Ether anesthesia frequently is required to carry out this method, especially if opisthotonos is present. One cubic centimeter of a 25 per cent solution of magnesium sulphate should be injected to each 20 pounds of body weight. The second dose should be smaller, about 0.8 cc to each 20 pounds of body weight. Only 0.5 cc of a 25 per cent solution to each 20 pounds of body weight should be used in a child. However, Meltzer³⁶ quotes that Kocher advises against the use of magnesium sulphate as a routine in children. The doses advised above are merely suggestive and are given as a working basis. The dosage should be decreased or increased until the desired effect is produced, that is, the relief of exhausting spasms. Magnesium sulphate should never be given in sufficient amount to completely relax the patient. It should be stopped when the relaxation is sufficient to permit feeding and to bring rest and comfort to the patient.

The only serious danger in the employment of magnesium sul-

phate seems to be the danger of respiratory paralysis. This effect may be relieved by calcium chlorid which reverses the action of the magnesium sulphate and brings back the tetanic spasms. A 2.5 per cent solution of neutral calcium chlorid in normal saline should be given slowly, intravenously, until the respiration is improved. The effect usually is seen within thirty seconds.

Ten to 15 cc of a 2.5 per cent solution of calcium chlorid given *intramuscularly*, and repeated if necessary, may slowly neutralize the unfavorable respiratory effect of the magnesium sulphate without causing the spasms to recur, and this method is advisable in less severe conditions. Joseph and Meltzer³⁷ have found that physostigmin in 1 mg. doses is sufficient in combating this respiratory depression. Artificial respiration, especially the intratracheal insufflation of Meltzer and Auer may be necessary. In respiratory failure following the intraspinal use of magnesium sulphate calcium chlorid does not act to overcome the complication, and Meltzer³⁵ advised that the spinal canal be washed out with Ringer's solution or with normal saline solution. Meltzer and Lucas³⁸ have shown that magnesium salts are eliminated to a great extent through the kidneys. The use of magnesium sulphate may cause urinary retention by paralysis of the muscles, according to Kocher³² and others. Hyaline casts may appear in the urine. (Peck³⁹ and Gates.⁴⁰) These complications disappear early and are temporary. The intravenous injection of magnesium sulphate produces considerable hyperglycemia with a mild glucosuria. This, however, is a temporary effect, and is no contraindication to the use of magnesium salts. (Meltzer.³⁶)

Meltzer^{35, 36} advised the employment of magnesium sulphate in the treatment of tetanus as follows:

1. The subcutaneous method every six hours, as a routine.
2. If severe spasms, employ the intraspinal method and repeat if needed.
3. If an element of immediate danger, use the intravenous method.
4. If the intraspinal or intravenous methods are not practical, give intramuscular magnesium sulphate with ether anesthesia.

The magnesium sulphate should be used boldly, but one should be ready to combat the complications. These complications cannot be considered as serious objections to the use of magnesium sulphate, as we are dealing with a very dangerous and fatal disease, and heroic methods must be employed. Furthermore, the serious complications can be combated in this method, better than when other sedatives are used. Kocher,³² after great experience with the use of magnesium sulphate in tetanus, is enthusiastic in advising its use. Robertson³³ recommends the method highly, and says "there is no such array of evidences for any other sedative." Pribam,⁴¹ in October, 1916, reviewed 148 articles in the Teutonic literature, and concluded that magnesium sulphate is the best

palliative for the treatment of tetanus. Buzello⁵³ states that magnesium sulphate is the best remedy to alleviate spasms and the general reflex excitability.

Magnesium sulphate should not replace the use of tetanus antitoxin. As has been previously stated, there is no evidence that magnesium sulphate has any effect on tetanus toxin, either free or combined. Furthermore, it generally is accepted that antitoxin has very little, if any effect, on toxin combined with nerve tissue. However, it is very important to give tetanus antitoxin freely and early, in order to neutralize the toxin in the circulation, and at the site of origin and to prevent further combination of the free toxin with nerve tissue, for the toxin does not produce tetanic symptoms when circulating in the blood, and acts only when it reaches the nerve cells. Thus the antitoxin acts to prevent the further progress of symptoms, and stops the further attack of the toxin on the nerve cells. The antitoxin may be given by the subcutaneous, intravenous, intraspinal or the intramuscular route. Park and Nicoll⁴² are ardent advocates of intraspinal serum, and report better results by this method. However, they also use serum intravenously and sedatives. Ashhurst,⁷ Bruce,⁴⁴ Andrews⁴⁵ and Golla⁴⁶ also favor the intraspinal method. Stone⁴⁷ recommends the use of serum in tetanus as follows: First day, 20,000 units, intravenously (20,000 units, intraspinally); second and third days, 20,000 units, intravenously (20,000 units, intraspinally); eighth or ninth day, 10,000 units, subcutaneously or intramuscularly; a total of about 125,000 units in adults. The use of serum lessens the mortality mainly by stopping the supply of toxin to the nerve tissue. As the intraspinal method generally requires anesthesia, it probably is better to try the subcutaneous and intravenous methods of administering the serum first. If the patient is getting worse or the condition is desperate serum should be used at once by the intraspinal route.

Anaphylactic shock may occur after the use of tetanus antitoxin, but death from this complication is unknown according to Ashhurst.⁷ Stone⁴⁷ quotes that the British war statistics report that it occurs in 2 per cent of intraspinal injections, in 6 per cent of intravenous and in 0.2 per cent of subcutaneous injections. Ten minims of epinephrin chlorid usually relieve the symptoms of anaphylaxis. Serum rashes occur in 40 to 50 per cent of the cases. Calcium lactate, $\frac{3}{4}$ gr., given intravenously, usually relieves the condition.

In addition to the use of serum and sedatives, the local treatment of the wound is very important. The wound should be opened and foreign bodies should be removed. Aërobic conditions should be maintained. Balsam of Peru locally applied to the wound has been ardently advised by Kreuter⁴⁸ and Ritter.⁵⁹ As shown by Ashhurst⁷ and Vaillard,⁴⁹ symbiosis with other bacteria, and other factors are necessary for the production of toxin by the tetanus

bacillus or tetanus spores. Speed⁶⁰ states that pure tetanus spores, free from toxin, injected into an animal are harmless in the absence of toxin, and the spores are devoured by the leukocytes. Anything which acts to prevent the leukocytes from getting to the spores permits the toxin to be developed and to produce symptoms. Secondary infection, necrotic tissue, blood clots and foreign bodies, all favor the development of toxins, interfere with the action of the leukocytes and supply anaërobic conditions.

Tincture of iodine not only acts as an excellent preventive of secondary infection, but seems to have some specific effect against tetanus toxin locally. MacConkey and Zilva⁵¹ and Teale and Embleton⁵² have showed that iodine mixed with tetanus toxin lessened the effect of the toxin. Kuemmell⁵³ states that tincture of iodine applied to wounds almost always prevented the development of tetanus in veterinary practice. Ashhurst⁷ and Tullidge⁵⁴ also emphasize this value of tincture of iodine. The well-known efficacy of iodine in preventing infection in accidental wounds and the apparent neutralizing effect of the iodine on tetanus toxin seems to indicate that its use locally is based on sound reasoning. As it is well established that tetanus toxin travels up the peripheral nerves, it seems rational to inject 5000 units of antitoxin about the wound of origin of the tetanus, with the idea of blocking the toxin.

In this connection, we desire to present 8 recent consecutive cases of acute tetanus, all of which recovered under treatment with magnesium sulphate and antitetanic serum.

Case Reports (by Dr. Smith). CASE I.—Mrs. L. L., aged sixty-eight years, was sent to the Lutheran Hospital by Dr. Reinhold Speer, June 25, 1922. She gave a history that her jaw became locked four days before admission. She had spasms in her throat and could not swallow. The patient had an abscessed tooth about three days before the symptoms began, and presented a complete prolapse of the uterus, with ulceration of the parts. The incubation period was not definite, as the point of origin was uncertain. On admission, the patient had extreme trismus, with rigidity in the neck and legs. The recti muscles were so rigid that they felt like steel plates. The temperature was 99.4° F. and the pulse was 120. She had not been able to take food or drink for several days. The patient was given 3000 units of antitoxin and 30 gr. of chloral hydrate at once. Ten thousand units of antitoxin were given intravenously and 16 cc of a 25 per cent solution of magnesium sulphate were given every five hours. On the next day, June 26, the condition was much improved. The spasms in the jaws, legs and recti muscles were distinctly lessened. The patient could take food and water, and had slept fairly well during the night. On the next day, June 27, the patient could open her jaws fairly well, and was

quite comfortable and free from spasms. Twenty thousand units of antitoxin were given. On the following day, June 28, three days after admission, the magnesium-sulphate injections were stopped, as considerable local irritation was occasioned by the injections. The next day, June 29, the muscles were again quite rigid and painful, so that the magnesium-sulphate injections again were employed and 20,000 units of antitoxin were given intravenously. After a few hours the patient was sleeping, and her condition was decidedly improved. On June 30 the injections of magnesium sulphate were stopped again. The rigidity increased somewhat, but was relieved by the further employment of magnesium sulphate. On July 3, eight days after admission, 1500 units of antitoxin were given subcutaneously. The patient returned home, July 9, entirely relieved.

Comment. This was a very severe case of tetanus in an old woman. Her condition had been getting worse daily. She received a total of 54,500 units of antitetanic serum. On three different occasions the spasms recurred after the magnesium sulphate had been discontinued, and each time the spasms were relieved again by injecting magnesium sulphate. The effect was so convincing that I feel certain that the recovery was largely due to the effect of the magnesium sulphate.

CASE II.—H. F. W., a male, aged thirty-five years, was referred to me by Dr. C. R. Hawker at the Alexian Brothers' Hospital, November 12, 1922. Nine days before, a drill passed through his left thumb while he was drilling an old mudguard of a motorcycle. The day before entering the hospital, that is, eight days after the injury, the man developed very painful clonic spasms in the muscles of the left side of the neck, which continued all night and during the next day, and the spasms could not be relieved by morphin. On entrance to the hospital the man could not swallow, the neck was rigid, the recti muscles were very tense and the jaws were somewhat rigid. The slightest stimulation caused severe painful clonic spasms in the left side of the neck and left shoulder. Fifteen hundred units of antitoxin were given subcutaneously and 20,000 units were given into a vein, and 16 cc of a 25 per cent solution of magnesium sulphate were ordered every five hours. The thumb was incised and serum was injected around the base. However, one dose of magnesium sulphate relieved the spasms, and the following morning the neck spasms were gone and the jaws and the recti muscles were relaxed. The man had slept well and was quite comfortable. The same evening another dose of magnesium sulphate was given, and 10,000 units of antitoxin were injected subcutaneously. The man was free from further spasms. On

November 21, nine days after admission, 3000 units of serum were given intramuscularly, and the patient was allowed to go home.

Comment. While rapid relief was present in this case, it undoubtedly was a case of local tetanus, progressing to general tetanus. A total of 34,500 units of antitetanic serum was administered.

CASE III.—F. C. W., a male, aged forty-one years, was referred to me at the Alexian Brothers' Hospital by Dr. J. J. Fitzgerald, December 16, 1922, with a history of having mashed his left index finger in an automobile spring three weeks before. The distal segment of this finger had been amputated, and the man had developed clonic spasms in his legs one week before admission. On entering the hospital, the patient had severe tonic spasms in his legs and recti muscles, with stiffness in the arms, and the least stimulation caused painful clonic spasms in the legs and abdomen, with opisthotonos. These symptoms had been getting worse for the previous six days, and the man could not lie in bed sufficiently quiet to permit a physical examination.

No trismus was present. Twenty thousand units of serum were given at once into a vein, and 16 cc of magnesium sulphate in 25 per cent solution were given subcutaneously every five hours. The wound in the finger which appeared to be healed was opened and considerable pus was found. It was kept open and cleaned out with tincture of iodine and hydrogen peroxide. On the following morning the symptoms were much improved. Some rigidity persisted, and short clonic spasms were caused by stimulation, but the man was fairly comfortable. Thirteen thousand units of serum were given into a vein. The next day, December 18, 20,000 units of serum were given intravenously and the magnesium sulphate was continued. Under this treatment, with average doses of morphine sulphate at times, the symptoms slowly improved day by day. The rigidity and clonic spasms continued to a lessened degree, but they were not considered severe enough to employ serum or magnesium sulphate, intraspinally. All medication was stopped, December 21, as the man presented symptoms of a bronchopneumonia and had a marked rash. The spasms increased somewhat, and magnesium sulphate was given again three times a day, beginning December 23, and again relieved the spasms. On December 24 10,000 units of serum were given into the muscles. Very short and slight clonic spasms of the recti muscles continued until December 26, when all spasms stopped. The man went home entirely relieved, January 13, 1923.

Comment. This was a very severe and exhausting case of well-developed tetanus. The effect of the magnesium sulphate was not so marked, but a gradual relief was effected. The improvement under subcutaneous injections of magnesium sulphate was satis-

factory, however, so that no other method of administration of the serum or magnesium sulphate was considered necessary. A total of 63,000 units of antitetanic serum was given in this case.

CASE IV.—V. K., a male, aged sixteen years, was seen in consultation with Dr. M. J. Glaser when the patient entered the Alexian Brothers' Hospital, February 7, 1923. The boy stated that his left index finger was lacerated by a piece of dirty, greasy metal from an automobile, about two weeks before entrance into the hospital. The wound had been sutured, but did not heal, and eleven days after the injury the boy noticed stiffness in his jaws and in his back. The following day he developed clonic spasms, which occurred on the slightest irritation.

On entrance to the hospital, which was three days after the onset of the symptoms, the patient presented marked opisthotonos, with retraction of the neck, board-like rigidity of the abdominal muscles, clonic and tonic spasms in the muscles of the jaws, spasm in the throat which prevented swallowing, stiffness in both legs and arms and greatly increased reflexes. The slightest stimulation would cause severe painful clonic spasms in the back, neck, jaws and abdomen. The symptoms had been progressing rapidly and the boy showed symptoms of great exhaustion.

Twenty thousand units of serum were given intravenously on entrance, and 5000 units were injected about the site of origin in the left index finger. The wound was opened, tincture of iodine was used freely and the wound was dressed so that air came in contact with it. Magnesium sulphate, 12 cc of a 25 per cent solution, were given subcutaneously every four hours.

The dose of magnesium sulphate was increased to 16 cc the evening of the same day, and 20,000 units of serum were given intravenously. The patient was resting easier and was able to swallow fluids freely during the evening.

On the second day, February 8, 10,000 units of serum were given intravenously, and the magnesium sulphate was continued in 16 cc doses every three hours. The spasms were less severe, and the boy was able to turn over in bed, but clonic spasms were frequent. However, a hypodermic injection of $\frac{1}{8}$ gr. of morphine sulphate permitted the boy to sleep.

On February 9 10,000 units of serum were given intravenously, and the magnesium sulphate was continued as before. On February 10 the boy's condition was much better; he could open his jaws wider, the abdominal spasms were less, the reflexes were less active and the boy was suffering no pain. The abdomen could be palpated without exciting spasms. Ten thousand units of serum were given intravenously. On February 11 and 12 the spasms were somewhat increased. The magnesium sulphate had been given at greater intervals. Ten thousand units of serum were given intra-

venously, February 11. The magnesium sulphate was again given at three-hour intervals, and on the evening of February 12 the spasms were lessened, but the boy was uncomfortable and exhausted. A subcutaneous injection of $\frac{1}{4}$ gr. of morphin sulphate permitted a restful sleep.

On February 13 the condition was much improved, the jaws were more relaxed, the abdominal muscles were soft and the legs were flaccid. Strong stimuli did not tend to cause spasms. From February 14 to 19 the condition improved. The clonic spasms became less in severity and frequency and disappeared. Some tonic spasms persisted, but the boy was comfortable. However, small doses of morphin produced restful sleep. Magnesium sulphate was given twice daily during this time. February 18 to 20 the clonic spasms increased, but they were controlled by increasing the magnesium sulphate. From February 21 to 24 the boy sat up in bed. Occasional jerks occurred in his arms and legs, but disappeared when the magnesium sulphate was given. On February 24 the boy was up in a chair. No spasms were present. He gained strength and gradually improved. On February 27 10,000 units of serum were given intramuscularly. The boy left the hospital, March 4, 1923, apparently entirely cured.

Comment. This was a very severe case of tetanus with considerable exhaustion. A total of 85,000 units of antitetanic serum was given. On several occasions the value of the magnesium sulphate was demonstrated when the spasms increased while the magnesium sulphate was discontinued, and further injections again controlled the spasms.

This case illustrates the marked effect of average doses of morphin when the patient is under the influence of magnesium sulphate. This point has been emphasized also by Gwathmey,⁵⁷ who states that combining the effect of magnesium sulphate with morphin sulphate, increases the value of the morphin from 50 to 100 per cent.

Painful exhausting spasms were relieved, and sleep occurred after $\frac{1}{8}$ to $\frac{1}{4}$ gr. doses of morphin on several occasions. Such doses of morphin in the absence of the relaxing effect of magnesium sulphate are powerless to control tetanic spasms. Furthermore, it seems that it is not necessary to push the effect of the magnesium sulphate to complete relaxation, and hence near the danger point. It is necessary only to control the spasms sufficiently to prevent exhaustion, at which point average doses of morphin may produce restful sleep.

Case Reports (by Dr. W. E. Leighton). **CASE V.**—H. B., male, aged twelve years, was seen in consultation with Dr. H. L. Nietert when the patient entered the Lutheran Hospital, July 10, 1922,

with a history of having shot himself in the index finger, July 3. He had been seen by a doctor, but no prophylactic antitetanic serum had been given.

On July 8 he began to complain of a stiff neck, and it was thought that he had a cold. On July 9 he was unable to open his mouth on awakening, and the jaw became fixed, but he had no convulsions. On admission to the hospital a small wad was removed from the finger with a curette. The cavity was sterilized with carbolic acid, irrigated with peroxide of hydrogen and packed with gauze, and a moist dressing was applied. Clonic contractions, involving the muscles of the jaw, neck and back were observed at this time. The temperature was 101° F.; pulse, 120; respiration, 36. During the day 20,000 units of antitetanic serum were given subcutaneously, and 10,000 units were given intravenously, with bromides and chloral hydrate.

The following day he was decidedly worse. He had a spasm, lasting ten minutes. He breathed heavily. During an attack he ground his teeth and frothed at the mouth. Opisthotonos was pronounced. During the day he had 25,000 units of antitetanic serum subcutaneously, intravenously and intraspinally, and subcutaneous injections of magnesium sulphate were begun. The temperature was 104° F., by axilla.

On July 12 spasms occurred every half hour during the night. The lips were blue and the breathing was shallow. During the day 40,000 units of antitetanic serum and 90 cc of magnesium sulphate were given subcutaneously. He was delirious at times. The following day the patient seemed better. Spasms occurred at longer intervals. He had one severe convulsion, lasting five minutes. Thirty thousand units of antitetanic serum and 90 cc of magnesium sulphate with chloral hydrate and $\frac{1}{8}$ gr. of morphin sulphate were given.

On July 14 he had one severe convulsion, lasting twenty minutes. The temperature was 102° F. As there was no improvement, it was decided to administer 2 cc of a 25 per cent solution of magnesium sulphate, intraspinally. Within two hours there was a decided improvement. There was marked relaxation of muscles and the patient felt better.

On July 15 and 16 he received 2 cc of the magnesium sulphate solution, intraspinally, and continued to show marked improvement. On July 17 he was so much better that it was decided to omit the intraspinal magnesium sulphate, but he was given 30,000 units of antitetanic serum and the subcutaneous injections of magnesium sulphate were kept up. During the night he had the most severe convulsion of all, and his condition was alarming. Magnesium sulphate, 2 cc, was given intraspinally, and within two hours relaxation had taken place. On July 18 relaxation was complete, and patient could turn on his side voluntarily. From this time on

the patient continued to improve, but 2 cc of a 25 per cent solution of magnesium sulphate were given intraspinally, and 5 cc subcutaneously, every four hours.

Muscular spasms, slight in character, kept up for several days, however, and did not entirely disappear until July 25. After this date the patient was up and about and was discharged, August 2, free from symptoms, except for an internal strabismus of the left eye.

Comment. This was an acute case of tetanus of five days' onset. The patient received in all 245,000 units of antitetanic serum and 815 cc of magnesium sulphate solution. He had 113 hypodermic injections without infection. In spite of the large doses of antitetanic serum, no improvement took place until the magnesium sulphate was given intraspinally, and after five intraspinal injections of 2-cc doses of magnesium sulphate the patient began to show improvement, and the convulsions were practically abolished.

I believe that without the use of magnesium sulphate, we would have lost this patient. The boy is perfectly well today, one year later.

The following 3 cases were from the services of Dr. Leighton and Dr. C. F. Sherwin at the St. Louis City Hospital.

CASE VI.—On July 13, 1922, a colored boy, aged fourteen years, was admitted to the City Hospital, complaining of stiffness in the neck and shoulders, with a history of having shot himself in the left index finger on July 4, 1922. The wound had been dressed, but no antitetanic serum had been given. Symptoms began on the eighth day. The left index finger was amputated. The muscles of the neck and abdomen were rigid, but there was no trismus. A well-marked convulsion occurred on the operating table. Thirty thousand units of antitetanic serum were given.

On July 14, the temperature was 106° F., and increased muscular rigidity and frequent convulsions were noted. On July 15, there was slight relaxation. Twenty thousand units of antitetanic serum were given. On July 16, attempts at opening the mouth caused convulsions. Nine thousand units of antitetanic serum were given. On July 17, 30,000 units of antitetanic serum were given. The abdomen seemed more relaxed. On July 18, 20,000 units of antitetanic serum were given. The patient was somewhat better. On July 19, 10,000 units of antitetanic serum were given. The patient did not feel so well, and refused to eat or drink. Trismus was marked. The head and neck bent backward, and the neck was rigid. On July 20, the patient refused to eat, as eating and drinking produced spasms. Marked rigidity of the neck and abdomen

was present. On July 21, 10,000 units of antitetanic serum were given. There was no improvement on July 22.

On July 23, 3 cc of 25 per cent solution of magnesium sulphate were given intraspinally, and relaxation of the muscles of the back and abdomen was noticeable within a short time. On July 24, the patient could move about with ease. The muscles were less rigid, and from this time the patient continued to improve until he was discharged. On August 2, he was up and about the ward, and appeared to be entirely cured.

Comment. This was a case of acute tetanus with an onset after eight days. Rigidity of the muscles continued in spite of 130,000 units of antitetanic serum. Relaxation appeared following 3 cc of magnesium sulphate intraspinally, and did not recur.

CASE VII.—A. W., aged forty-two years, entered the St. Louis City Hospital, August 25, 1922, with a history of having stepped on a nail, eighteen days previously. Five days before entrance he began to have a difficulty in mastication of food on account of the stiffness of the jaw. Three days later he was obliged to go to bed because of dyspnea. Stiffness of the muscles of the abdomen, neck and the arms was marked. On entrance the arms were flexed across the chest and were rigid. The neck was rigid and could not be flexed. Excursions of the chest were limited, and the abdomen was rigid. There was an anxious look on his face, and the jaws were locked. The legs were not rigid and motion was not restricted. A small scar, which was not tender, on the sole of the right foot, was excised under ether. The wound was cleansed with tincture of iodine, and a dry sterile dressing was applied. Sixty thousand units of antitetanic serum were given subcutaneously and intraspinally, and 6 cc of a 25 per cent solution of magnesium sulphate were administered subcutaneously.

The second day he received 20,000 units of antitetanic serum and 20 cc of magnesium sulphate subcutaneously in divided doses. There was no change in his condition. Spasms occurred at intervals of fifteen to twenty minutes. The third day there was some improvement. Spasms occurred only on external irritation, such as a sudden noise. He received 10,000 units of antitetanic serum and 20 cc of magnesium sulphate were given subcutaneously. On the fourth day the jaws became somewhat relaxed, and he was able to open them slightly. Ten thousand units of antitetanic serum and 20 cc of magnesium sulphate were given subcutaneously. On the following day he was much better, and the abdominal muscles were relaxed. From this time he steadily improved, and was able to move about in bed on the eighth day. No medication was given after the tenth day, and all muscular motions were normal on the fourteenth day.

Comment. The onset in this case took place on the thirteenth day. He received 90,000 units of antitetanic serum and 156 cc of a 25 per cent solution of magnesium sulphate, subcutaneously.

CASE VIII.—J. D., aged twelve years, entered the St. Louis City Hospital, September 11, 1922, with a history of having cut his foot on a rusty piece of tin, twelve days previously. Three days before admission he noticed that he could not open his mouth, and his jaws appeared stiff, and the following day he could not bend his neck. Muscular twitchings began on the day of entrance. On admission he had rigidity of neck, abdomen, back and legs. Opisthotonos was marked, and the respiration was labored. The jaws were locked. Under ether anesthesia the scar on the sole of the foot, which was partially healed, was excised. Fifty thousand units of antitetanic serum and 12 cc of a 25 per cent solution of magnesium sulphate were given subcutaneously. During the day convulsions were frequent, and were excited by the least external irritation.

On the second day he received 30,000 units of antitetanic serum and 12 cc of magnesium sulphate. During the day the patient said he felt better and could open the mouth slightly and he was less rigid. On the third day the patient could turn slowly in bed, he felt better and expressed a desire to eat. During the day 20,000 units of antitetanic serum and 18 cc of magnesium sulphate were given subcutaneously. The patient was very nervous. On the fourth day he received 12 cc of magnesium sulphate and 20,000 units of antitetanic serum. Slight opisthotonos persisted. During the next few days he improved rapidly, and was up and about the ward, with no abnormal symptoms present on the tenth day. He was able to open his mouth to the full extent on the seventh day.

Comment. The onset in this case was on the ninth day following the injury. He received 140,000 units of antitetanic serum and 78 cc of a 25 per cent solution of magnesium sulphate subcutaneously. On account of extreme nervousness he had an occasional hypodermic of morphin sulphate in average doses.

Discussion. We are convinced that the use of magnesium sulphate played a very important rôle in our success in these 8 consecutive cases of tetanus. They were all distinct cases of acute tetanus, and prophylactic serum had not been given in any case.

Magnesium sulphate should be used in proper amounts to produce results. The subcutaneous method should be tried first, but if results are not prompt, the intraspinal method should be employed. This condition was found in Cases V and VI, where prompt relief followed the intraspinal use of magnesium sulphate, after the subcutaneous method did not give satisfactory results.

As illustrated in Case IV, it is not necessary to produce complete relaxation by pushing the magnesium sulphate near the danger point. After the spasms have been relieved sufficiently to prevent exhaustion average doses of morphin often will complete the relief and permit restful sleep.

There can be no routine in the use of magnesium sulphate. The dosage and method can be determined only by close personal and frequent observation of the patient. Magnesium sulphate cannot cure tetanus in the last stages. It cannot restore completely exhausted tissues. Its effect purely is to prevent exhaustion and to keep the patient comfortable and alive and permit nourishment, until the toxin can be separated from the nerve cells and eliminated.

Use of antitetanic serum during the disease is necessary in order to counteract free toxin and to prevent further combination of the toxin with nerve cells. Thus, the effect of the neutralizing antitetanic serum and the sedative effect of the magnesium sulphate are necessary for the cure of tetanus.

Summary. The rational treatment of tetanus should be carried out as follows:

1. Prophylactic antitoxin, subcutaneously in all suspicious wounds, repeated again after ten days, especially if suppuration is present, or if an operation is to be performed.

2. Antitetanic serum should be given during an attack of tetanus. Intravenous administration may be satisfactory. Intraspinal serum should be employed in severe cases or where improvement is not satisfactory.

3. Spasms should be controlled by the subcutaneous injection of magnesium sulphate. In urgent symptoms or when the subcutaneous method fails intraspinal or even the intravenous route should be employed. Morphin sulphate, in addition to magnesium sulphate, may aid at times. Careful personal observation is necessary in order to judge the dosage and method of administration of magnesium sulphate.

4. The wound of infection should be opened and cleaned, and air should be allowed to reach it. Tincture of iodine should be used locally. Serum should be injected at the site of the wound to block the progress of the toxin.

5. An intramuscular or subcutaneous injection of serum should be given on the eighth or ninth day after the beginning of the treatment, in order to keep up the prophylaxis.

6. Fluids and nourishment should be supplied, and careful nursing is essential.

REFERENCES.

1. Nicolaier: Inaug. Diss. Göttingen, 1885.
2. Kitasato: Deutsch. med. Wchnschr., 1889, 15, 635.
3. v. Behring and Kitasato: Deutsch. med. Wchnschr., 1890, 16, 1113.

4. Donati: Arch. ital. di chir., 1919, 1, 1.
5. Kuemmell: Berl. klin. Wehnschr., 1916, 53, 414.
6. Tulloch: Proc. Roy. Soc., London (Series B), 1917-1919, 90, 529.
7. Ashhurst: Arch. Surg., 1920, 1, 407.
8. Speed: Med. and Surg., 1918, 2, 499.
9. Stauff: Zentralbl. f. Chir., 1916, 43, 916.
10. Bungart: Zentralbl. f. Chir., 1916, 43, 917.
11. Vernoni: Gazz. d. osp. e d. clin., Milano, 1917, 28, 955.
12. Montois: Ann. de l'inst. Pasteur, 1916, 30, 330.
13. Courtois-Suffit, Giroux and Fernan-Widal: Prevention of Tetanus, Paris, Masson et Cie, 1916.
14. Gessner: Jour. Am. Med. Assn., 1918, 71, 867.
15. Ochsner: Jour. Am. Med. Assn., 1918, 71, 870.
16. Chavasse: Bull. et mém. Soc. de chir. de Paris, 1917, 43, 1249.
17. Hutchings: Ann. Surg., 1919, 50, 52.
18. Bérard and Lumière, Lyon chir., 1915, 12, 404.
19. Du Bouchet: Bull. et mém. Soc. de chir. de Paris, 1917, 43, 924.
20. Bergell and Levy: Therap. d. Gegenw., 1904, 45, 396.
21. Murphy: Jour. Am. Med. Assn., 1904, 43, 460.
22. Hercher: München. med. Wehnschr., 1915, 62, 1126.
23. Meltzer: Am. Jour. Physiol., 1900, 3, 9.
24. Meltzer and Auer: Am. Jour. Physiol., 1905, 14, 366.
25. Meltzer: Med. Record, 1905, 68, 965.
26. Meltzer and Auer: Am. Jour. Physiol., 1906, 16, 233.
27. Meltzer and Auer: Jour. Exper. Med., 1906, 8, 692.
28. Blake: Surg., Gynec. and Obst., 1906, 2, 541.
29. Logan: Jour. Am. Med. Assn., 1906, 46, 1502.
30. Miller: AM. JOUR. MED. SCI., 1908, 136, 781.
31. Hessert: Surg., Gynec. and Obst., 1909, 9, 145.
32. Kocher: Corr.-Bl. f. schweiz. Aertze, 1912, 42, 969; 1913, 43, 97; 1915, 45, 1249.
33. Robertson: Arch. Int. Med., 1916, 17, 677.
34. Straub: München. med. Wehnschr., 1915, 62, 341; *ibid.*, 1915, 62, 25.
35. Meltzer: Lancet, London, 1915, 1, 1330.
36. Meltzer: Jour. Am. Med. Assn., 1916, 66, 931.
37. Joseph and Meltzer: Jour. Pharm. and Exper. Therap., 1909, 1, 369.
38. Meltzer and Lucas: Jour. Exper. Med., 1907, 9, 298.
39. Peck: Proc. Soc. Exper. Biol. and Med., 1913-1914, 11, 103.
40. Gates: Proc. Soc. Exper. Biol. and Med., 1913-1914, 11, 102.
41. Pribram: Jour. Am. Med. Assn., 1918, 71, 869.
42. Park and Nicoll: Jour. Am. Med. Assn., 1914, 63, 235.
43. Nicoll: Jour. Am. Med. Assn., 1915, 64, 1982.
44. Bruce: Lancet, London, 1917, 1, 680.
45. Andrews: Lancet, London, 1917, 1, 682.
46. Golla: Lancet, London, 1917, 1, 686.
47. Stone: Jour. Am. Med. Assn., 1922, 78, 1939.
48. Kreuter: Beitr. z. klin. d. Infek., 1916-17, 5, 189.
49. Vaillard: Jour. State Med., London, 1914, 22, 513.
50. Speed: Surg., Gynec. and Obst., 1916, 22, 443.
51. MacConkey and Zilva: Brit. Med. Jour., 1916, 1, 411.
52. Teale and Embleton: Jour. Path. and Bacteriol., 1919, 23, 50.
53. Kuemmell: Beitr. z. klin. Chir., 1915, 96, 421.
54. Tullidge: New York Med. Jour., 1916, 103, 1022.
55. Bruce: Brit. Med. Jour., 1917, 1, 118.
56. Weston and Howard: AM. JOUR. MED. SCI., 1923, 165, 431.
57. Gwathmey: Jour. Am. Med. Assn., 1921, 76, 222.
58. Buzello: Ztschr. f. ärztl. Fortbild., 1922, 19, 427.
59. Ritter: Berl. klin. Wehnschr., 1915, 52, 126.

OBSERVATION OF FAT DIGESTION FOR CLINICAL STUDY
AND PHYSIOLOGICAL DEMONSTRATION.

BY ANTHONY BASSLER, M.D., F.A.C.P.,

AND

J. RAYMOND LUTZ, B.S., M.D.,

NEW YORK.

A PROCEDURE is herewith advanced in which the digestion of fat as it takes place in the human body may easily be observed, one in which the admixture of fat with pancreatic juice and bile occurs *in vivo*, one of some value in clinical study, and of value in a physiological department.

These observations were made during a period of the work of studying pancreatic function which consummated in the test for pancreatic function which one of us has devised. The findings were made during the work of studying lipolytic action and were so interesting that they seem worthy of separate presentation.

PROCEDURE. In the morning, having taken no breakfast, the individual swallows the duodenal tube with the assistance of water. When the tip is well out in the duodenum (proven by fluoroscope) a few moments are allowed to elapse to permit the last of the water to leave the stomach. The patient then drinks about 60 cc of olive oil and lies on the right side. Gentle aspiration by means of a suction bulb and an intervening bottle of about 250 cc capacity is employed, which is kept in a water bath of 104° F. In an average time of nine minutes a characteristic return from the duodenum appears. As soon as the oil returns and at frequent intervals a drop is placed on a slide without cover glass and observed for fifteen to thirty minutes. A warm stage is preferred but the phenomena to be described also occur in the cold. The high dry objective is used in order to get best details.

EMULSIFICATION. This consists of oil with duodenal juice and bile. The oil will be found to have been more or less emulsified—the first stage of fat digestion. Usually the first return of the emulsion is coarse but may be fine, even finer and more uniform than the fat globules in milk which is looked upon as a perfect emulsion. In all periods of the aspiration the return contains the emulsion which gets finer. Investigation suggests that the emulsification of fats in the body takes place, not by agitation as occurs commercially when making an emulsion, but chemically. The bile, or certain constituents of it, acting on the oil, produces the emulsion. At various times an occasional globule has been seen very actively to break up into smaller globules by rolling along with pseudopods trailing after it which break off into a number of much smaller globules. When formed, the emulsion remains so for some time;

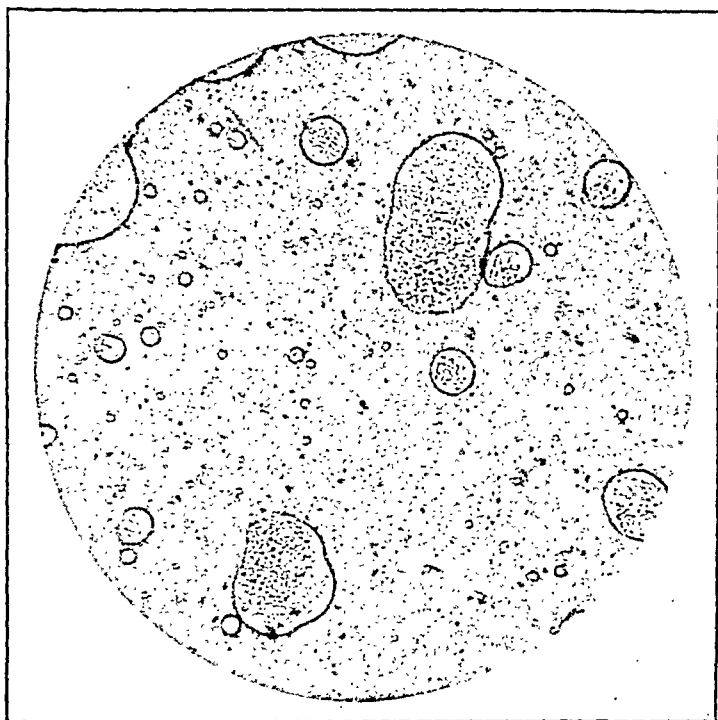


FIG. 1.—Showing stippling.

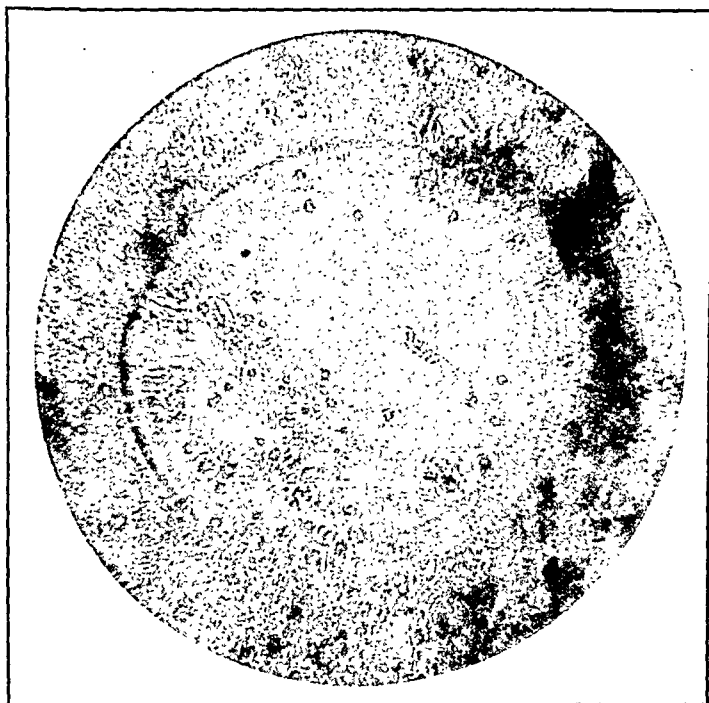


FIG. 2.—Showing rivulation.

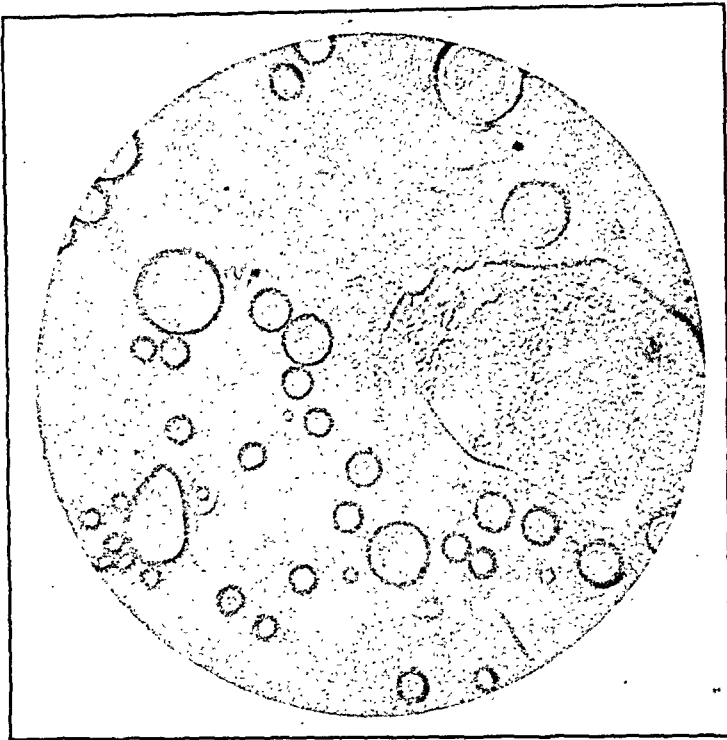


FIG. 3.—Showing rapid dissolution of the surface of the globule.

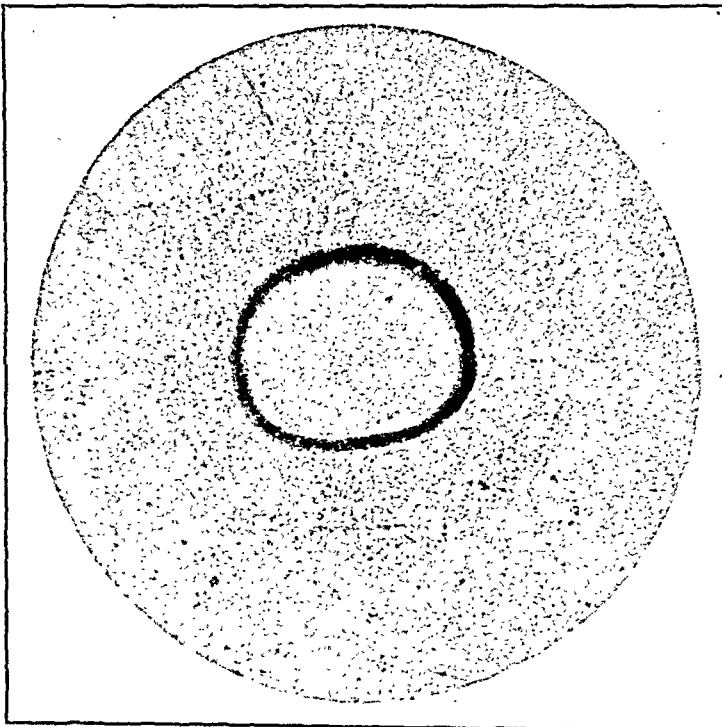


FIG. 4.—Showing corona of soap and pseudopod.

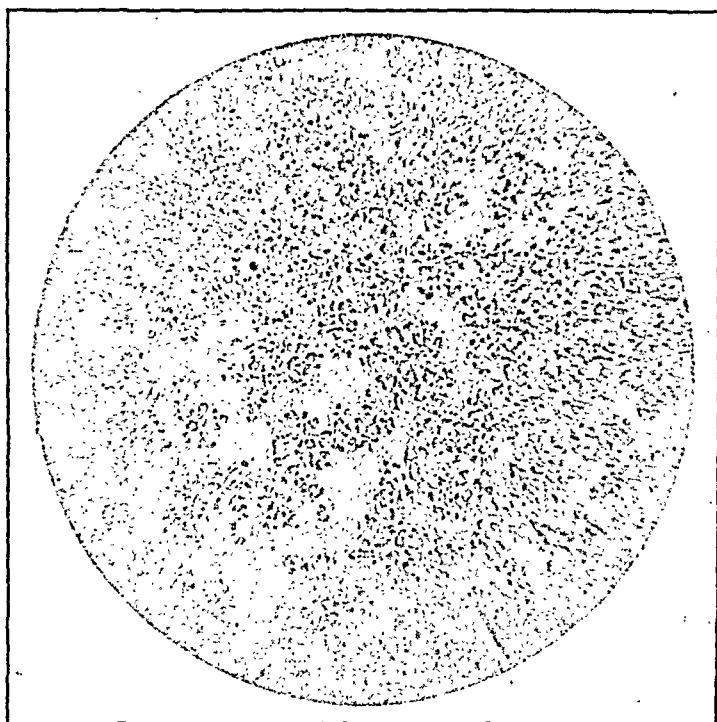


FIG. 5.—Complete soap formation.

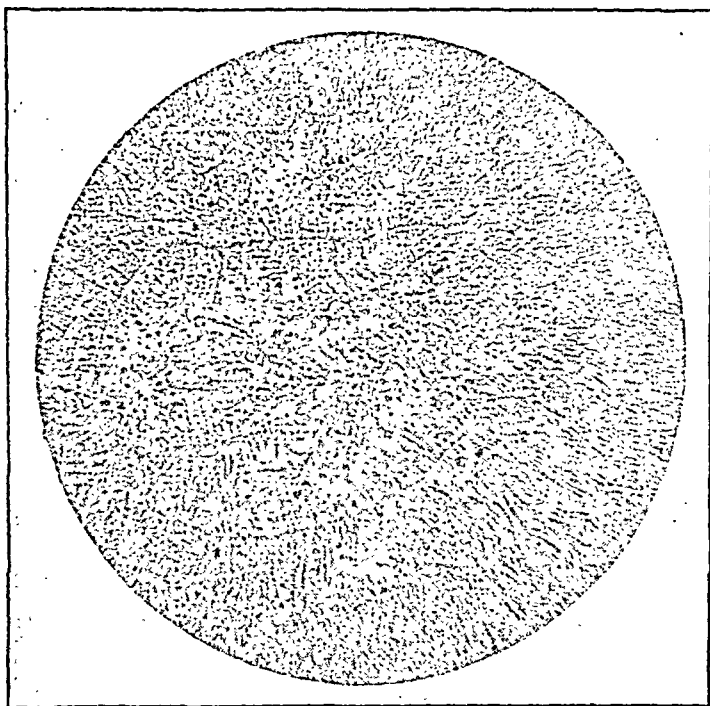


FIG. 6.—End-stage of fatty acid formation (palmitic acid crystals).

these provisions make it possible for lipolytic action on the fat to continue in the easiest and most vigorous ways. This emulsification continues in the duodenum whether the contents are acid or alkaline and will continue outside until an intense acidity occurs from fatty acids. As the emulsion becomes more acid the globules coalesce and the oil forms a layer on the top of the mixture. Watching the globules coalesce through the microscope shows the whole field in active commotion. At certain periods this is so lively that the whole field will change every few seconds.

SAPONIFICATION. The phenomena here may be described as what may be observed within and without the fat globule. Usually these are found going on together or one globule in the field may show one phase and another the other.

Watching the individual globules, even those of considerable size, shows as the first change one of two phases. The first may be designated as striation, and consists of a series of wrinkles or striæ, running more or less parallel across the globule, the process being gradual and progressive. These are very active when present but may not be observed in some returns. It probably is produced by some tension effect plus the action of lipase on the surface of the globule. These striæ are gradually increase in number and size and appear like wrinkles on a shriveled apple. The striæ are visible in the process of formation for fifteen seconds to two minutes when the globule turns over, the striæ or wrinkles disappear and a clear homogeneous globule of oil is again seen. This process of striation and returning to the original form may take place over and over for an indefinite number of times but after one to fifteen minutes they go on to the next stage, that of stippling. This may follow striation but can occur as an initial performance. One notices here a few granule-like bodies forming on the surface of the globule and in a short time the entire globule becomes that way. The whole interior of the globule may be in active motion, the globule itself being at rest. When the stippling or granulation has reached a certain stage of density or concentration they slide off to the periphery of the globule and into the surrounding medium. The process of stippling and casting off of particles of material repeats many times until the globule is about one-half the original size or smaller. Waves of refractive material occasionally are seen running concentrically toward the periphery of the globule and into the surrounding liquid and appear like waves of melting butter running off from a ball of butter being heated from above. These waves of material as they leave the globule disappear and are dissolved in the surrounding medium. This material, we believe, is soluble soap. This phenomena we have designated "rivulation." During the stippling process, bud-like projections of soaplike amebic pseudopods may form, become solidified, and either break off from the remainder of the globule or remain attached to it. More buds form at various

points around the periphery (spherical) and go through the same process. Due to budding, rivulation and the slipping off of the stippled surface to the periphery, there soon accumulates a corona of solid, irregular immobile material which we believe to be soap. The field then contains free masses of this soap as some of it slips away from the parent globule. Rarely granular material may be seen to form within the globule and suddenly burst through the wall of the globule with considerable force. The corona of soap is very frequently many times the size of the original globule which has become smaller. After the formation of the corona the process stops, probably because of concentration of (fatty) acids. If the slide is allowed to stand for some time (to dry) most of the field will be found to be composed either of masses of soap or covered with the feather-like palmitic acid crystals. A clear, colorless, oily fluid remains which does not dry and is probably glycerine. Not infrequently globules will be seen to coalesce suddenly with a colorless irregular shaped oily material seemingly laking or being dissolved into it and losing its original yellow, oily consistency. This is a sudden complete conversion of the globule into soluble soap which is dissolved. Not infrequently the globules will from fully filled fat globes break up by the globules disappearing, leaving large masses of soap and fatty acid crystals and a certain portion of colorless liquid (glycerine).

Perhaps the most interesting of all of the phenomena are the soap projections that occasionally occur from a complete fat globule. These occur in one of two ways. The first is the sudden protrusion of a portion of the capsule that closely resembles the pseudopodium of an ameba, but differs from it in that the globule remains quiet. Two or more of these may occur from the sides of the same globule. Apparently they are portions of soap that have been excluded from the neutral fat of the globule. The second form is the extrusion of the soap from the globule in small particles, these generally adhering to the sides of the fat globule, their number accumulating.

FATTY ACID FORMATION. This is observed as a part or accompaniment of the phases described above. Here and there the crystals are met with, and if a slide is allowed to stand for an hour or two they will be observed intermingled with small deposits of soap and usually a large drop of glycerine on one part of the slide.

Summary. The phenomena described can be used as a clinical test for lipase activity. It is, of course, not quantitative in any definite sense but when one has made these observations a number of times a judgment of value is soon acquired.

For physiological demonstration in medical schools and elsewhere there is no easier, striking and quickly performed demonstration of lipolytic action of the pancreas than this. Enough material can be obtained from one individual tested to supply sufficient material under the microscope for a large number of students.

PRIMARY CANCER OF THE LIVER*

BY JULIUS FRIEDENWALD, M.D.,

AND

HIRAM FRIED, M.D.

(From the Gastro-Enterological Clinic of the Department of Medicine of the University of Maryland.)

THE variety of primary carcinoma of the liver renders this affection of sufficient interest to warrant the report of even a single case. It is generally admitted that data concerning the incidence of this disease to 1870 are unreliable; inasmuch as up to this period the metastatic types were not definitely differentiated from the primary forms. In Hanseemann's¹ 258 cases of carcinoma of the liver, four (1.5 per cent) were primary. Eggel² noted 163 cases of primary carcinoma of the liver up to 1901 and Goldzieher and von Bokay³ observed 18 cases in 6000 autopsies (0.3 per cent). In 1911 Karsner⁴ reported 9 cases and in 1913 Winternitz⁵ 3 cases occurring in 3700 autopsies at the Johns Hopkins Hospital (0.08 per cent) while in 1923 Clawson and Cabot⁶ report a single case in 5100 autopsies at the University of Minnesota. Lichty and Richey,⁷ in 1922, report 3 cases observed by themselves and note that the incidence of this disease varies in different clinics from 0.13 to 1.3 per cent with an average of 0.5 per cent in the collected autopsy reports. Torland⁸ reported 10 cases in 10,000 autopsies performed for all causes.

Report of Case. A. N., single, female, aged fifty-two years, consulted us April 28, 1921. She complained of abdominal discomfort especially located in the upper right abdomen, which had been annoying her for several years, but which had gradually become more aggravated during the past year. In addition there has been pressure and distention in the lower abdomen at times with occasional nausea, acidity of the stomach, eructations, bitter taste in the mouth, and constipation. The patient has not had any previous serious illnesses and her family history was unimportant. She had lost 10 pounds in weight.

On physical examination, there was evidence of loss of flesh, and the scleræ and skin present a slight icterus. Her weight was 106 pounds; the pulse, temperature and respirations were normal. The blood-pressure was 140/80. The heart and lungs presented no abnormalities. The abdomen was soft, extremely relaxed; the liver extended slightly below the costal arch and there was a slight degree of tenderness in this area as well as in the lower abdomen. The spleen was not palpable. The urine was normal, with the

* Presented at the Meeting of the Association of American Physicians, Atlantic City, N. J., May 7, 1924.

exception of a trace of bile, which it contained on a number of examinations. The tests for albumin, sugar and casts were always negative. The Wassermann blood test was negative. The hemoglobin was 80 per cent; red blood cells numbered 4,200,000; leukocytes, 6400. The gastric contents, following an Ewald test breakfast, revealed a total acidity of 53; free HCl, 42. The stool was of medium size, semisolid and fairly light in color and contained a slight quantity of mucous and undigested food matter; blood was not present.

The non-surgical biliary drainages presented turbid bile, somewhat greenish in color, but containing large fractions of "B" bile, with cholesterin crystals and mucus, and revealed in addition a definite colon infection.

The roentgen-ray report was as follows: Prolapsed fish-hook stomach, actively contracting and pulled over and held in the upper right quadrant; no defects; duodenal cap not deformed; colon prolapsed and spastic; cæcal stasis.

The diagnosis arrived at was cholecystitis with possible beginning cirrhosis of the liver.

Under a six weeks' rest cure in addition to frequent non-surgical biliary drainages, the patient improved markedly in health with relief from all abdominal distress. All evidence of the slight jaundice heretofore noted had disappeared; she made a gain of 10 pounds in weight, and with the exception of occasional headaches, appeared to enjoy normal health.

On April 22, 1922, a year following her first visit, she again returned with a history of having a drawing discomfort in the upper right quadrant of the abdomen with distention during the preceding two weeks, together with a progressively increasing jaundice. On examination, the liver was found apparently smaller than at the previous examination, and a large quantity of free fluid was noted in the abdomen. The skin and scleræ were deeply jaundiced.

Operation was advised and performed on the following day. About 500 cc of a straw colored fluid escaped from the abdominal cavity; the liver was found small, hard and definitely cirrhotic and contained numerous nodules. An omentopexy was performed. The patient quickly recovered from the affects of the anesthetic and apparently was doing well for the first twenty-four hours. She then lapsed into a deep coma, developed fever (101° to 102°) and died on the third day following operation.

Autopsy (No. 71). Performed one hour and forty minutes after death.

Anatomical Diagnosis. Primary carcinoma of the liver, cirrhosis of liver, hemorrhagic ascites, jaundice, right sided pleurisy with effusion, pulmonary edema, acute bronchopneumonia, chronic nephropathy, chronic pericarditis, hour-glass stomach, cervical polyp, anemia, emaciation and edema of the extremities.

Protocol. The body is that of a white woman, 163 cm. in length; rigor mortis has set in. There has been evident loss of weight as is shown by the looseness of the skin and the loss of subcutaneous fat. The scleræ are very yellow. Nose and mouth are negative. Both jugulars are distended and stand out prominently. There is a network of dilated veins over both shoulders. None are seen on the abdomen. There are 2 abdominal incisions; (1) An upper right rectus, through which two cigarette drains and a rubber tube projects; (2) a low midline incision starting at the umbilicus and extending 10 cm. toward the pubis.

The *lungs* show a marked congestion and edema with fresh pleural adhesions and areas of bronchopneumonia. The mediastinal glands are as large as army beans and black. There are no gross areas of new growth.

The *abdominal cavity* contains a large amount of blood-tinged yellow fluid. The omentum is sutured outside the abdominal cavity in the midline incision to the sheath of the rectus muscle. It is red and granular in this portion but not strangulated. The jejunum looks edematous and its walls are thick and rubbery, as if hypertrophied. This condition extends to the ileum which seems normal. The appendix is long, thickened and attached to a band of adhesions, which extends from the lateral abdominal wall to the cecum. The stomach has a constriction in its middle portion, and is edematous like the jejunum. The duodenum is greatly dilated; C-shaped and also very edematous.

The *liver* is smaller than normal; measures 22 by 14 by 7 cm. and weighs 1000 gm. The surface is coarsely granular with nodules studded over the surface varying in size from a few millimeters to several centimeters. The left lobe is almost separated from the rest of the liver by a deep fissure, and consists almost entirely of one large nodule, measuring 8 by 2 cm. The nodules vary in color from a very deep brown to a light opaque yellow, which resembles fat. In certain areas, the tumor invades the lumen of the portal veins and bile ducts. Where liver parenchyma still remains, it is of a deep greenish-brown or a grass-green color. Gray translucent bands of fibrous tissue can be seen both surrounding the nodules and permeating between lobules of liver parenchyma.

It is interesting to note that extrahepatic nodules were conspicuous by their absence. The lymph nodes showed evidence of chronic inflammation, but no new growth was made out either in the gross or microscopical examination.

Microscopical Examination of Liver. The portions of liver parenchyma not involved by new growth are the seat of a marked cirrhotic process. This is irregularly distributed and involves mainly the periportal spaces. Where new growth is present, the cirrhosis is still more marked. Here and there in the cirrhotic areas are clumps of round cells. The tumor assumes a trabecular arrangement,

sometimes presenting as long strands of single cells resembling normal liver parenchyma; elsewhere, as columns of three or four cells abreast. As has been frequently observed, the tumor cells are easily differentiated from normal liver: (1) By their smaller size; (2) by their increased affinity for hematoxylin; (3) by their lack of pigment (hemosiderin); (4) by the occasional presence of mitotic figures.

Discussion. Primary carcinoma of the liver may occur at any period of life; more frequently in males between the fortieth and sixtieth years. Griffith⁹ collected 57 cases in children from the first to the sixteenth years of life; Danzie¹⁰ 23 cases under two and a quarter years and Rolleston¹¹ 32 under ten years. The following table taken from Yamagiwa¹² indicates the occurrence of this disease as to sex and age.

Age.	Liver-cell cancer.		Bile-duct cancer.	
	Eggel.	Yamagiwa.	Eggel.	Yamagiwa.
1 to 10 years	1	2	1	0
11 to 20 years	2	1	0	0
21 to 30 years	7	2	2	0
31 to 40 years	12	5	2	0
41 to 50 years	13	2	2	3
51 to 60 years	28	9	1	4
61 to 70 years	22	0	4	1
Over 70 years	8	0	1	0
Not indicated	0	6	0	7

	Liver-cell cancer.		Bile-duct cancer.	
	Male.	Female.	Male.	Female.
Yamagiwa	17 (80.95%)	4 (9.5%)	4 (50.0%)	4 (50.0%)
Eggel	65 (68.40%)	30 (31.6%)	6 (42.9%)	8 (57.1%)

According to Winternitz the malignant epithelial tumors of the liver may be divided into those arising from the bile ducts and those from the liver cells. The appearance of the bile pigment in distinguishing these types is only of relative importance inasmuch as while the bile stained nodules are ordinarily derived from the liver cells, tumors developing from small bile ducts may also have bile pigment contained within their lumina. They may be distinguished however, from a microscopical point of view, *i. e.* by their tendency to conform to the structure of the tissue from which they develop, the bile-duct cancers occurring as tubulo-adenomatous and the liver-cell cancers as trabecular structures.

The relation existing between primary carcinoma of the liver and cirrhosis has been a matter of considerable interest.

According to Winternitz's tables and analysis, a large proportion of cases of primary cancer of the liver are associated with cirrhosis and cirrhosis is definitely more frequently observed in cancers arising from the liver cells than in those from bile ducts. Karsner⁴ also agrees that cirrhosis is observed to some degree in almost all cases of primary liver cancer, and Pirie¹³ calls attention to the occur-

rence of cirrhosis as an associated factor in many instances of this disease in the natives of Africa infected with schistosomiasis, inasmuch as this form of infection has been proven to be a frequent cause of cirrhosis.

While the largest proportion of cases of cancer of the liver are associated with the annular type of cirrhosis, other forms as syphilitic or those due to echinococcus cyst infection occur.

A number of theories regarding the relation of cirrhosis to the new growth have been advanced. Certain observers maintain, that the two conditions occur entirely independently of each other, others that the cirrhosis is a causative factor or that the two diseases are a result of the same etiological factor and still others, that the cirrhosis is secondary to the tumor.

According to Winternitz the relation of cirrhosis to carcinoma can be best explained on the following bases. Due to injury, a destruction of liver tissue occurs on account of which fibrosis and regeneration takes place. This is followed by a production of hyperplastic nodules of liver cells and bile-duct structures, ordinarily observed in cirrhosis. These formations have the appearance of true adenomata. On account of the continuance of the injury the necrosis and regeneration continues, the cells lose their function and through an excessive proliferation develop into malignant growths. According to this investigator therefore, the nodular hyperplasias, often indistinguishable from true adenomata are the source of the carcinomatous growths, and therefore all cancers must develop through the benign or adenomatous stage.

While the multicentric development of the primary cancer of the liver has been maintained by many investigators (v. Heukelom,¹⁴ Travis,¹⁵ Goldzieher and Bokay,³ Yamagiwa¹²); others (Ribbert,¹⁶ Karsner⁴ and Winternitz⁵) hold that these growths are unicentric in origin.

Metastases are not very frequent, occurring mainly in the thoracic and mesenteric lymph glands, omentum, lungs and other parts of the liver. According to Eggel,² of 163 cases collected 40 presented no secondary involvement, 50 showed growths only in the portal and hepatic branches, 30 had metastases in the lungs and thorax, 18 in the lymph nodes and 9 involved the colon, pancreas, ovary, kidneys, omentum, thyroid and cranium, respectively. Catsaras¹⁷ was unable to ascertain but a single instance in which metastases were noted in several bones from primary cancer of the liver. He described a case with metastases in the head and neck of the femur. Ewing¹⁸ notes that extrahepatic metastasis occurs much earlier and is more frequent in biliary than in hepatic carcinoma. It is an interesting fact that in many instances of extrahepatic metastases in primary carcinoma of the liver, bile has been observed in these growths.

According to Ewing¹⁸ primary carcinoma of the liver may be

divided into 3 distinct groups: (1) The primary massive liver cells carcinoma; (2) the multiple liver cell carcinoma; (3) the carcinomatous cirrhotic forms.

The first variety occurs aside from the cirrhosis which may accompany this growth and but few symptoms are noted until near the termination of the disease. This growth represents a rapidly developing malignant form of solitary adenoma. It is met with as a large single yellowish friable mass in either the entire right or left lobes; metastases in various portions of the liver are not uncommon. The consistence of the mass is soft and as the result of an extensive liquefaction necrosis and hemorrhage a cystic formation may be produced with rupture into the peritoneum. The histological structure presents wide variation, but retains, at certain areas at least, its resemblance to liver cells. Ewing describes four distinct histological variations in structure: (a) Trabecular adenocarcinoma containing large granular acidophile cells as well as giant cells; (b) alveolar adenoma with areas consisting of groups of smaller granular epithelium surrounded by wide capillaries; (c) peritheliomatous areas containing capillaries surrounded by cubical granular cells, (d) diffuse carcinoma. In many of the necrosed areas the normal arrangement of cells disappears, and the growth consists of diffuse round or spindle cells with hyperchromatic nuclei.

In the second group—the multiple liver cell carcinoma—is classified the very malignant rapidly progressive forms in which cirrhosis is absent or is very slight. Ewing claims that no sharp division can be made however between this form, the solitary massive carcinoma, and carcinomatous cirrhosis forms. In this variety the liver is enlarged and presents many nodules which are grayish or bile stained, hemorrhagic or necrotic. Many of the smaller nodules are probably secondary. Metastases are infrequent but extensions to the diaphragm and gall-bladder are not unusual. Histologically, this form of carcinoma presents a number of variations, according to the area examined; these may be according to Ewing, trabecular carcinoma with giant cells, small alveolar carcinoma with many capillaries and diffuse carcinoma. Encapsulation of tumor masses is not noted. Clinically, this affection is extremely rapid in its course, in many instances terminating within a few weeks to a few months and at times the patient may succumb suddenly without having had any previous indication of a serious illness. Jaundice is not ordinarily observed but serous or bloody peritoneal effusions are not unusual. This affection is usually characterized by rapid emaciation and cachexia with enlargement of the liver and ascites.

The third group represents the carcinomatous cirrhosis forms. In this variety there is rapid increase in hyperplasia, invasion of veins and at times metastases. The growth is closely related to the cirrhosis and consequently the clinical signs are, in a measure, those

observed in this disease. The liver is ordinarily of the contracted type, but may be of normal size or greatly increased presenting multiple nodules often bile stained. The nodules may be extensive, numerous and usually involve the entire liver. In addition a definite portal cirrhosis is noted, and the nodules themselves are involved in connective tissue. It is not uncommon for the liver to present the typical appearance of hypertrophic cirrhosis. Microscopically, the liver presents an extensive replacement of parenchyma by adenomatous and carcinomatous nodules.

There is hyperplasia and hypertrophy of cell groups in the lobules. The cell groups enlarge into nodules, and produce atrophy by pressure on the remaining tissues. The cells of the growth are large producing thickened liver bands or the nuclei by increasing rapidly produce numerous smaller cells. Nuclear division of the amitotic type, giant-cell and syncytial masses, and fatty degeneration are conditions frequently observed. Cancerous cirrhosis, while usually noted in individuals over the fortieth year of life, is also found in young persons, previously in good health, gradually developing the symptoms of cirrhosis, *i. e.* jaundice and ascites. In fact the usual symptoms of cirrhosis precede the onset of carcinoma, which is finally revealed by the cachexia, progressive anemia, indigestion, hemorrhages, with a fatal termination within a few weeks or months. Clinically, there are but few distinctive signs of this affection; though at times the disease develops as a tumor formation with the growth in the region of the liver, and with the usual history of carcinoma in individuals previously in good health. In others the disease may be latent and may only be detected at autopsy in individuals succumbing to cirrhosis or other affections. In another class of cases the carcinoma is preceded by the usual signs of cirrhosis and finally terminates with the development of a rapidly growing tumor in the hepatic region. In all instances the presence of a carcinoma must be suspected by the rapid emaciation, secondary anemia and cachexia. Fever is not unusual in those instances with rapidly growing masses, especially in the terminal stages of the disease. Gastro-intestinal disturbances are common, and not infrequently dull dragging discomfort and pain in the right side and back. According to Torland⁸ icterus is present in 63 per cent of cases; ascites in 58 per cent; general edema in 41 per cent; splenic tumor in 32 per cent; fever in 14 per cent. Eighty-six per cent of the cases are associated to a more or less degree with cirrhosis.

The prognosis is extremely grave, and Hale White¹⁹ maintains that a fatal outcome usually occurs within four months following the first appearance of signs of malignancy of the liver.

REFERENCES.

1. Hansemann: Berl. Klin. Wchnschr., 1890, 27, 353.
2. Eggel: Beitr. z. path. Anat. u. z. allg. Path., 1901, 30, 506.
3. Goldzieher and v. Bokay: Virchows Archiv, 1911, 203, 75.

4. Karsner: *Arch. Int. Med.*, 1911, 8, 238.
5. Winternitz, Johns Hopkins Hosp. Rep., 1913, new series, No. 3.
6. Clawson and Cabot: *Jour. Am. Med. Assn.*, 1923, 80, 13, 909.
7. Lichty and Richey: *Ann. Clin. Med.*, 1922, 1, 165.
8. Torland: *Northwest Med.*, 1922, 21, 253.
9. Griffith: *AM. JOUR. MED. SCI.*, 1918, 155, 79.
10. Danzie: *Lancet*, 1922, 2, 228.
11. Rolleston: *Diseases of the Liver, Gall-Bladder and Bile Ducts*, 1905, p. 469.
12. Yamagiwa: *Virchows Archiv.*, 1911, 206, 437.
13. Pirie: *Med. Jour. South Africa*, 1921, 17, 87.
14. v. Heukelom: *Beitr. z. path. Anat. u. z. allg. Path.*, 1894, 16, 341.
15. Travis: *Johns Hopkins Hosp. Bull.*, 1902, 12, 108.
16. Ribbert: *Das Karzinom, Bonn.*, 1911; *Deutsch. med. Wehnschr.*, 1909, 35, 1607.
17. Catsaras: *Ann. de m d.*, 1921, 10, 295.
18. Ewing: *Neoplastic Diseases*, W. B. Saunders, 1919, 2d ed., p. 682.
19. Hale White: *System of Medicine (Allbutt and Rolleston)*, 1908, 4, 1, 215.

THE PATHWAYS OF THE MEDIASTINUM, THE LUNGS, AND THE PLEURÆ.*

By J. CURTIS LYTER, M.D.

ASSISTANT PROFESSOR OF INTERNAL MEDICINE, ST. LOUIS UNIVERSITY SCHOOL OF MEDICINE; VISITING PHYSICIAN TO ST. ANTHONY'S HOSPITAL AND TO THE ST. LOUIS CITY HOSPITAL, ST. LOUIS, MO.

To anyone with the opportunity to observe closely the inception, progress, and termination of active pulmonary tuberculosis, there comes a time when an experimental explanation of some of the observed phenomena is desperately sought. This has probably become more certain with the development of the technic and study of pulmonary stereoroentgenograms. While pulmonary stereoroentgenography has aided very materially in the clinical study of pulmonary diseases, it has, by its own merits, forced the clinician into some newer fields of thought.

One phase of chronic, progressive, pulmonary tuberculosis which has been especially attractive to clinical thought is the apparent migration of the tubercle bacilli from the primary lesion to other portions of the same or the opposite lung. This apparent migration is probably best observed, in a clinical way, by a study of serial stereoroentgenograms taken at regular intervals in those cases revealing a steady progress of the pulmonary pathology. During the clinical and laboratory study of these cases the sputum should be proved to be bacilli free, thereby excluding the possibility of aspirated secondary lesions confusing the situation. Under serial stereoroentgenographic observation, as well as by frequent physical examinations, one is frequently able to observe the development of lesions at various sites of the same or opposite lung, follow the prog-

* From the Department of Internal Medicine of the St. Louis University School of Medicine and St. Anthony's Hospital.

ress of the primary lesion noted at the initial examination to be in one apex only. The clinical and stereoroentgenographic observation of the development of multiple lesions throughout the one or other lung would appear convincing as to the migration of the organisms from the primary lesion to various portions of either lung.

A second solution which does not consider the migration of the organisms necessary is that in which multiplicity of the sites of the primary infection is taken as an explanation of the multiple lesions observed during the course of all fatal cases. To accept this solution one must believe that during the initial invasion of the organisms they were implanted at various sites in each lung and that from the primary implantation the multiple pathological lesions developed during the progress of the disease.

Regardless of the conception one may entertain regarding the pathway traversed by the organisms in gaining access to the lung, it probably remains true that there exists only one site of primary infection and that the lesions which successively develop throughout one or both lungs during the progress of the disease have their origin in the one primary lesion by reason of the migration of the bacilli from the primary lesion to various sites in the same or across the mediastinum into the opposite lung.

From the clinical point of view, the migration of the organisms seems certain but when the phenomena are viewed from the anatomical aspect the migration of the organisms seems altogether impossible. From this aspect the migration seems impossible because of the very structure of the pulmonary lymphatics which heretofore were considered the only pathways open to the migrating organisms. The work of Miller seems to prove conclusively the presence of valves in the lymph trunks passing through the septa of the secondary lobules. Near the lung periphery these valves point toward the pleura and would seem to be a direct injunction against the passage of any material from the pleural surface through the lymphatics into the lung substance. A second set of valves were described by Miller as being located in the lymph trunks near the hilum. These valves point toward the hilum and have been presumed to prevent the passage of any material from the hilum into the lung substance. From the presence of these two sets of valves the lung substance seems protected against the entrance of any material by way of the lymph trunks. If these valves do exist and have the function seemingly indicated by their anatomical structure and position, they should act as an impediment to bacteria or other material passing into the lung substance from the pleural surfaces, subpleural spaces, or mediastinum merely because they would seem to indicate a flow of lymph only from the lung substance toward the pleura or toward the hilum.

The results of Miller's work have been disputed by some very

able anatomists but his own plates are so very convincing as to lead one to the conclusion that such valves do exist.

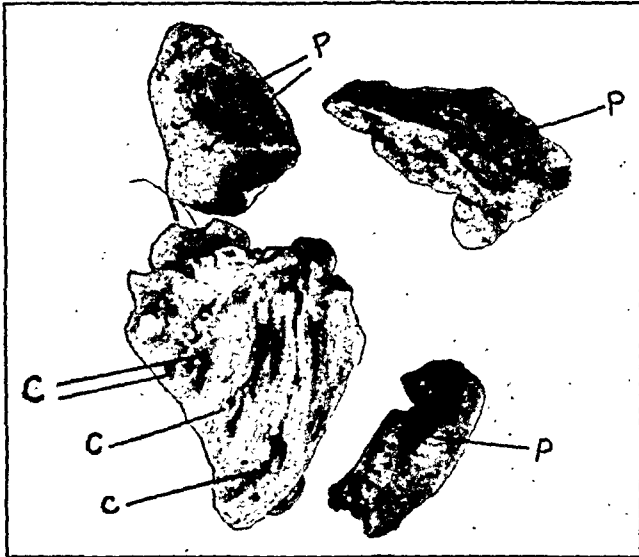


FIG. 1.—Showing masses of pigment beneath the visceral pleura indicated by *P*, and beneath the parietal *C*.

Experimental. Be the anatomy as it may, there are some phases concerning the clinical aspect of multiple lesions which, to the

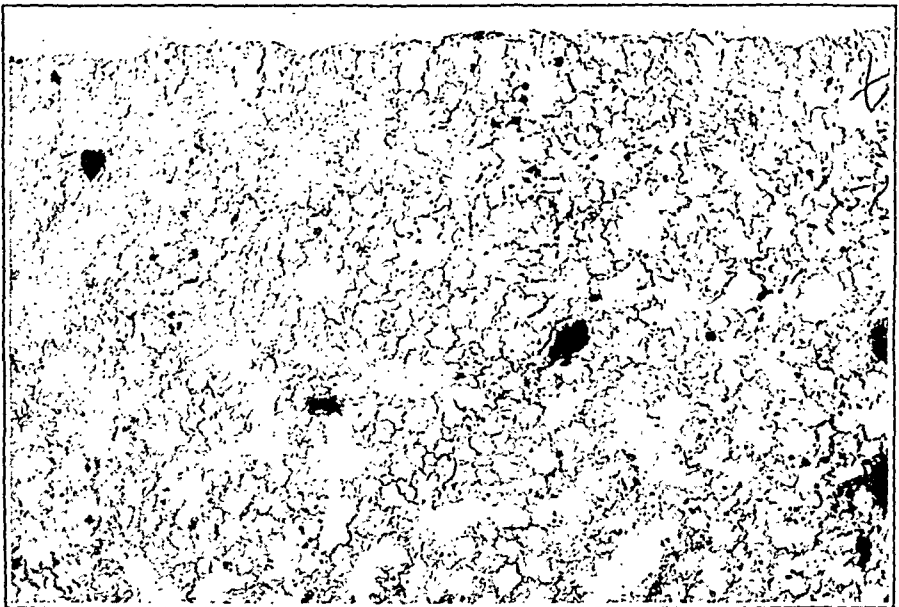


FIG. 2.—The left lung of a sheep whose mediastinum has been injected with India ink. Showing numerous accumulations of the pigment.

clinician, seem to demand an experimental investigation. This investigation was undertaken in the laboratories of St. Anthony's

Hospital to determine the probability of material passing from the mediastinum into the substance of the lungs and the probability of the same kind of material passing from the pleural surface into



FIG. 3.—Right lung of the sheep described in Fig. 2.

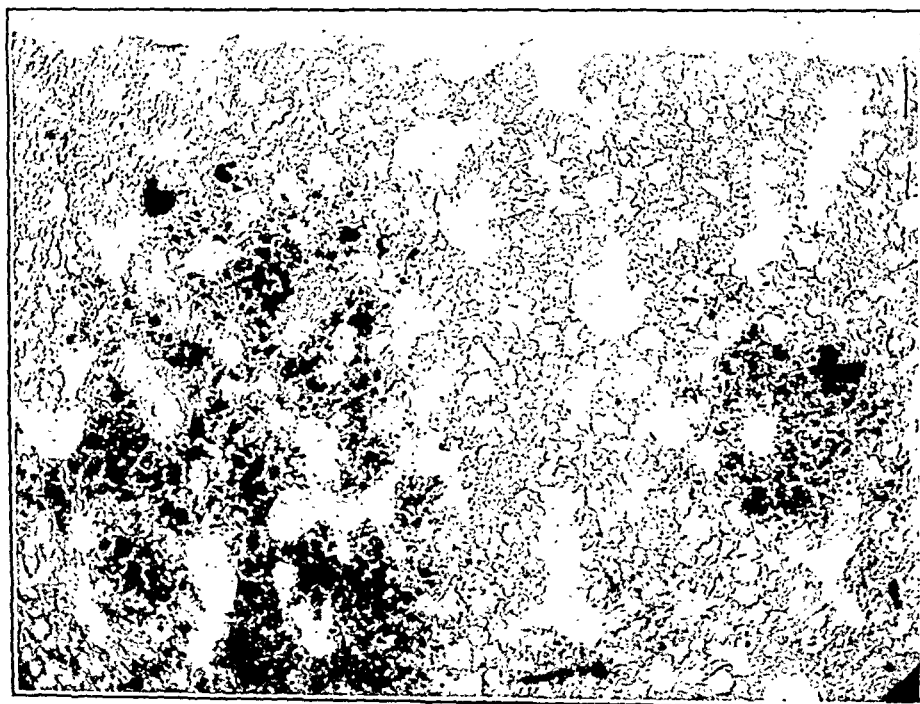


FIG. 4.—Right lung of a sheep where the right pleural cavity had been injected with India ink.

the lung substance. We were not primarily concerned about the pathways or means taken by the materials in passing into the lung substance, but were only concerned with the question of the existence of such a passage. For purposes of the investigation guinea-

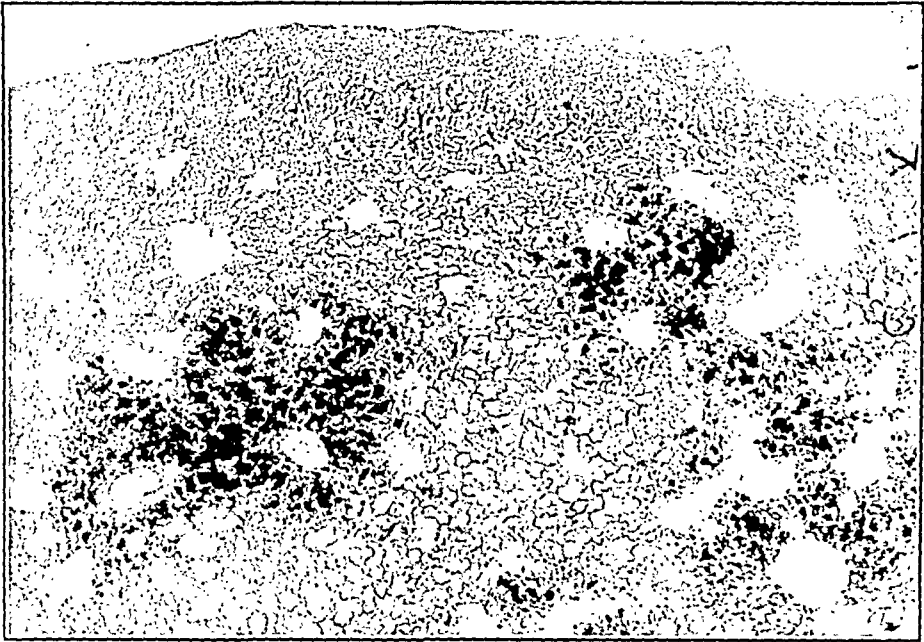


FIG. 5.—Left lung of a sheep where the right pleural cavity was injected with India ink.

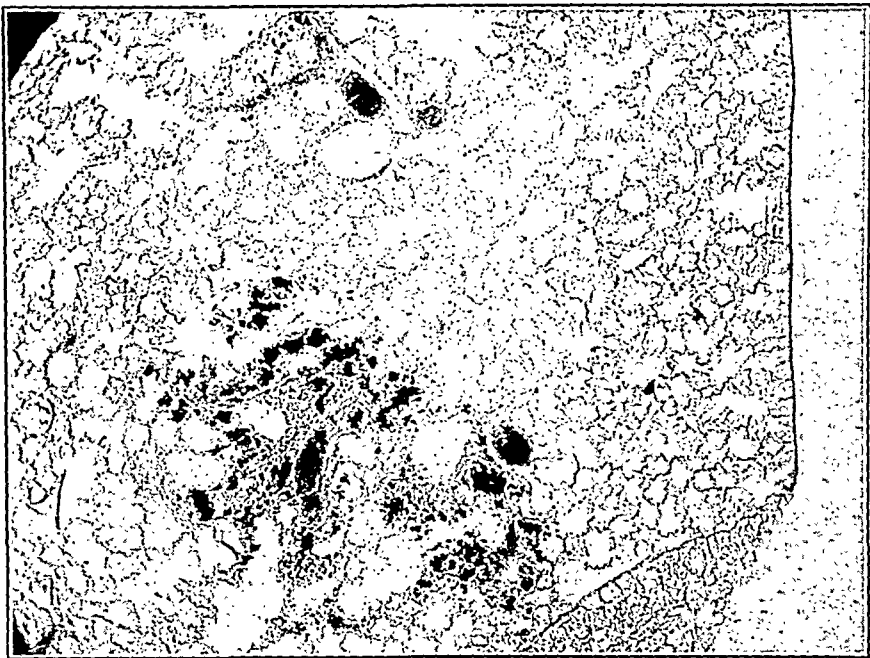


FIG. 6.—Left lung of a rabbit where the mediastinum was injected with India ink.

pigs, rabbits, and sheep were employed. Guinea-pigs and rabbits are known to have very thin pleura and poorly developed septa of

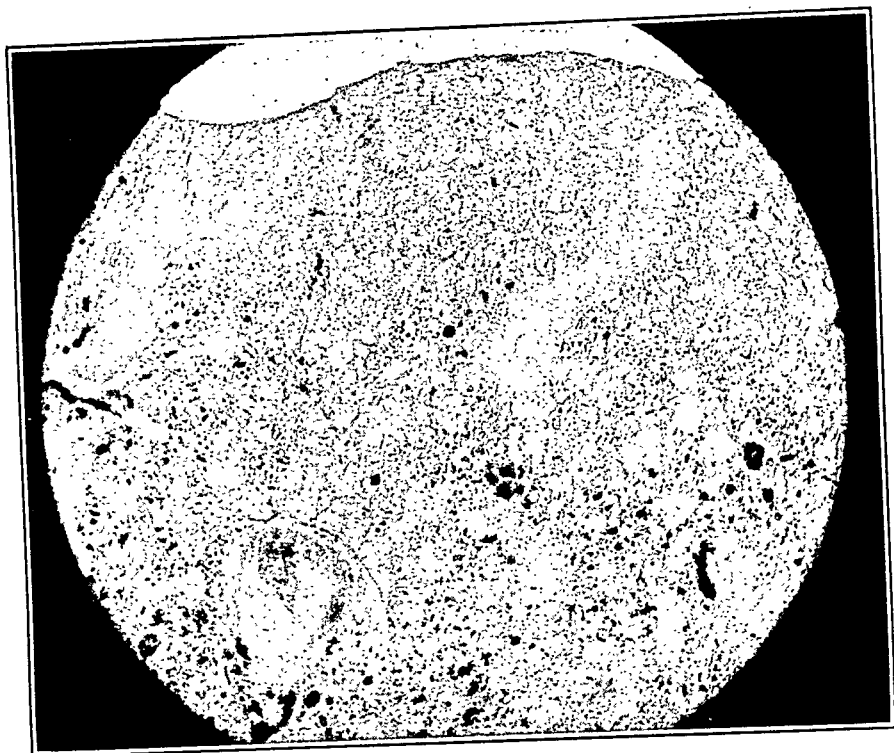


FIG. 7.—Right lung of the rabbit described in Fig. 6.

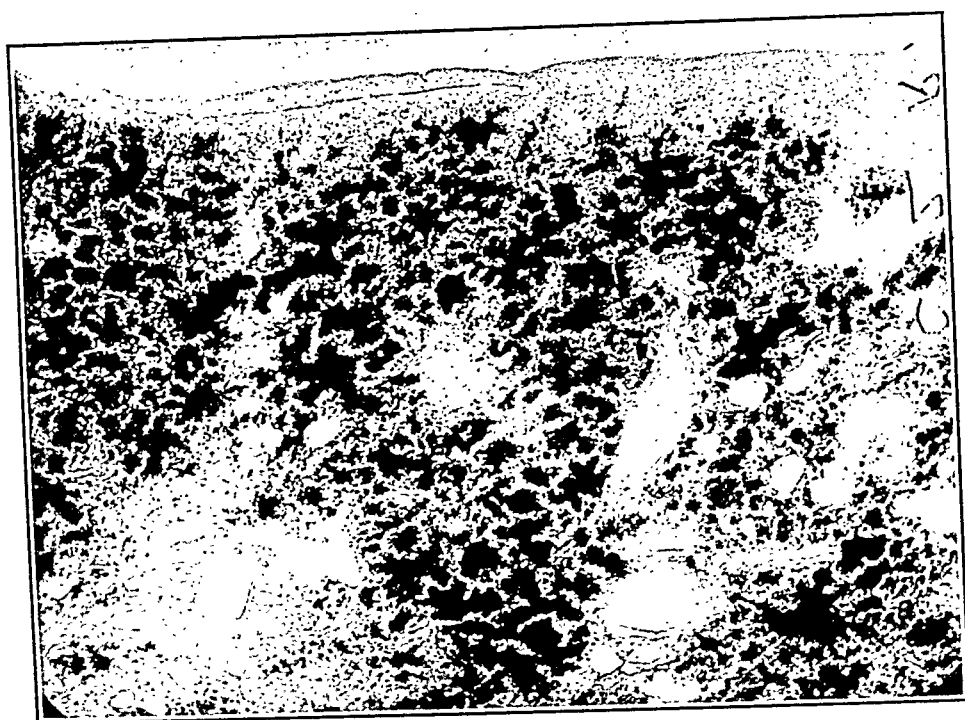


FIG. 8.—Right lung of a rabbit where the right pleural cavity had been injected with India ink. Showing large quantities of India ink throughout the lung structure.

the secondary lobules. Sheep, on the other hand, have a thick pleura and well developed septa, very similar to those conditions found in the human lung. The first set of investigations was to determine the transmissibility of material from the mediastinum into the lung substance. The material chosen was, during the early investigation, an aqueous suspension of charcoal. This was found to wash out of the tissues during the process of staining and in that way prevented a microscopical study of its distribution, consequently its use was given up and in its place India ink, which proved most satisfactory and permits of microscopical study after staining, was employed. Chinese vermilion was also employed in some experiments, but was abandoned because it produced such violent local reactions as to interfere greatly with normal local function. After numerous attempts it was found possible to inject a small quantity

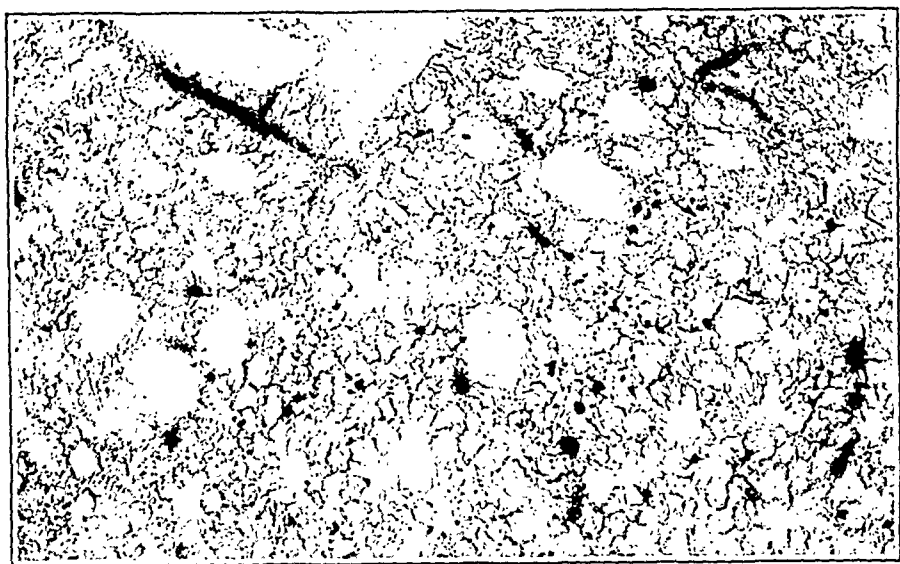


FIG. 9.—The left lung of the rabbit described in Fig. 8.

of material into the mediastinum at the bifurcation of the trachea—thus placing the material in contact with the lung hilum.

The injection of India ink into the mediastinum in this fashion represented the first complete set of investigations and for this purpose guinea-pigs, rabbits, and sheep were employed. A series of guinea-pigs were taken and one-fourth of a cubic centimeter of India ink was injected into the mediastinum once each week for six weeks and the animals autopsied two weeks after the last injection. One-half cubic centimeter was used for the rabbits and they were autopsied four weeks after the sixth weekly injection. For the sheep, about 2 cc were employed and the autopsies were performed six weeks after the sixth weekly injection. The longer time given to the rabbits and sheep after the last injection was an arbitrary decision, as was also the amount of material used. It was thought

to be the part of wisdom to employ larger amounts of materials and to permit a longer time to elapse between the final injection and the autopsy in the sheep and rabbits because of the thick pleura known to be present in these animals and because of their greater size. Following the autopsy, a gross and microscopical study was made of the lungs, thoracic wall, heart, diaphragm, and the tissues of the neck, liver and spleen. In the examination a careful search was made for the presence of the injected material in the tissues, its distribution, and its tendency to collect in masses. All of the animals guinea-pigs, rabbits and sheep, revealed the same findings, which were as follows: There was pigment scattered throughout each lung. This pigment revealed a strong pleural drift, with at places large collections beneath the pleura. Within the lung tissue the greater quantity of the pigment was in the intercellular spaces and in the spaces around the bloodvessels and bronchi, a small quantity being found in those cells called macrophages. There were large collections of pigment within the parietal pleura on each side, but notably none beneath the diaphragmatic pleura and none in the liver or spleen. The same gross findings were present in those animals upon which a suspension of charcoal was used; but, as stated previously, a microscopical study of the tissues for the charcoal is impossible because it is removed by staining.

The result of these experiments proved that pigment, such as India ink or charcoal, can pass from the mediastinum into the lung substance and into the spaces beneath the parietal pleura.

For the second part of the investigation, another series of guinea-pigs, rabbits and sheep were taken and the same quantity of material with the same time intervals as was used in the mediastinum cases was again employed, the site of the injection in these cases being the right pleural cavity, due precaution being taken that the lung tissue was not injured. After the autopsies in these cases a search for the pigment, grossly and microscopically, was made as in the mediastinum cases. Again it was found that the pigment was scattered throughout each lung, the quantity in the left lung being as great as that in the right. The distribution was similar in all respects to that found in the mediastinum cases. The pigment was found in the tissues of the mediastinum and beneath the parietal pleura on each side. Again no pigment was found beneath the diaphragmatic pleura or in the liver or spleen. The findings were the same in all three types of animals; and, as before, those cases where charcoal was employed revealed the same general, gross distribution of charcoal as did the others of the India ink.

The results of this experiment indicated that India ink or an aqueous suspension of charcoal placed in the right pleural cavity can migrate throughout the right lung, into the mediastinal tissues, throughout the left lung, and into the subpleural spaces of the parietal pleural.

It is altogether probable that bacteria can thus migrate from one portion of the lung to other parts and even into the opposite lung.

Studying the stained specimens with a high-power lens one can see that most of the pigment found in the lung tissues lies in the intercellular spaces and in the spaces around the bloodvessels and the bronchi. None is observed within the large lymph trunks or the bloodvessels and a very small portion, relatively, in the macrophages.

I cannot close the discussion of this experimental work without acknowledging my great indebtedness and gratitude to Sister M. Florina, Chief of the Laboratories of St. Anthony's Hospital. Her assistance was invaluable in sectioning and staining the tissues.

Summary. The observation herein described demonstrates beyond question that rather coarse material, such as an aqueous suspension of charcoal, can through some pathways migrate from one portion of the thoracic cavity to another portion and throughout the respiratory tissues. The mechanism of this migration depends probably more upon the physiology of the pulmonary respiration with the almost constant movement of the intrapulmonary fluids than upon phagocytosis or lymph flow as it was formerly conceived. This phase of the question is still under investigation in our laboratories and the results of that investigation will be forthcoming.

In succeeding discussions we shall attempt to show the influence of the reticulo-endothelial system upon the distribution of [the pigment.

A NEW VASCULAR SIGN OF DEATH.

BY MORRIS H. KAHN, M.A., M.D.,

NEW YORK.

(From the Department of Cardio-vascular Diseases, Beth Israel Hospital, New York City.)

ALTHOUGH the transition from life to death is a gradual process, certain phenomena take place so definitely at the borderline that we consider them as signs of death.

The phenomenon that I wish to point out as a significant sign of death consists of certain changes in the appearance of the small vessels, especially the veins, all over the body. To speak of these as capillaries would not be consistent with the facts in human beings if we limit capillaries to only those vessels of such small caliber as will admit red blood cells to pass through in single file.

It is the circulatory changes alone that so significantly and so promptly give undeniable evidence of death. Normally, the small vessels are constantly filled, with slight variations in volume as the result of pulsation. Postmortem, the column of blood in the vessels,

sustained and solid, undergoes a change which manifests itself within a limited time.

This change consists of the formation of transverse interruptions in the red color of the vessels, giving the appearance of division or striation of the blood column. These interruptions, often only few in number, are apparently chiefly in the veins and occur both near the disc and distant from it. They occur less constantly in the smaller arteries. While looking at the fundus of the eye, or during the course of frequent repeated examinations of it, or at any accessible superficial venules, one notices from time to time, a distinct variation in the length of one or the other striation. This can be made more evident by turning the head of the subject from side to side or by compressing the vessel momentarily. It can be still more accentuated by pressure upon the eyeball, in both these ways modifying the retinal intravascular pressure. Firm external pressure upon the eye empties the veins in the region of the disc and also the central artery. Upon relaxation the vessels refill to their former capacity. These manipulations for a time after death alter the size of the interruptions considerably. After about one hour no spontaneous alterations in size are noticeable. After a longer time, *i. e.*, about three hours, the vascular striations are no longer influenced by manipulation and pressure. These phenomena are sometimes more manifest in one eye than in the other. These observations have since been confirmed by animal experiments and present a physiological basis for their occurrence.¹

When the animal dies, the movement of blood in the smaller vessels and capillaries at first comes to a sudden stop. Then the corpuscles clump slightly and shortly begin to move forward in the normal direction. This movement, at first noticeable in the capillaries, extends to the venules and there is a slow and gradual progression of blood toward the larger veins. The appearance is as if no blood entered the capillaries from the arterial side and that a milking process, akin to peristalsis, swept the corpuscles onward toward the vein. When the process is complete it may be found that here and there in the capillary net a few clumped corpuscles are locked as if the constriction of the vessel had failed to carry on the last of its contents.

These changes occupy varying lengths of time in different animals. They may develop completely in a few minutes or they may last half an hour or more. The completeness with which the vessels empty is also a varying factor. Sometimes, particularly in old and debilitated animals, the blood may not be moved at all; sometimes the field is swept absolutely free of blood but more often a few clumps of corpuscles are left stranded, particularly in the venules. The stagnation of these clumped corpuscles is the significant feature which I consider the early appearing sign of death.

¹ Hooker, D. R.: *Am. Jour. Physiol.*, 1920, 54, 30.

That these events are not alone evidences of peripheral changes in the circulation but also central may be shown by the fact that in a large portion of human dying hearts, the venous ends, that is the auricles, continue to beat for a long time after the ventricles, and in that way effect changes in the peripheral circulation, especially in the venules.

It is known that blood remains uncoagulated for a long period inside of uninjured bloodvessels. Finally, of course, intravascular coagulation takes place. Segmentary in occurrence with consequent shrinking of the fibrin, this leads to the formation of intercoagular spaces containing serum. The clots in the vessels contract, and thus separate in places from each other, leaving between them the serum which is expressed in the process of congealing. In a number of cases the intercoagular intervals were not observed. In these cases, probably clotting of the distal arterial column took place *en masse*; and the serum that otherwise formed the intercoagular interval, was expressed murally. In a few of the cases presenting choked discs no intercoagular intervals were found. Here the above-enunciated explanation is the more maintainable, drawing support from the idea that the central pressure favored coagulation *en masse*. It is likely that it is the adherence of the fibrin to the vessel wall that finally prohibits variation by pressure, of the size of the intercoagular spaces.

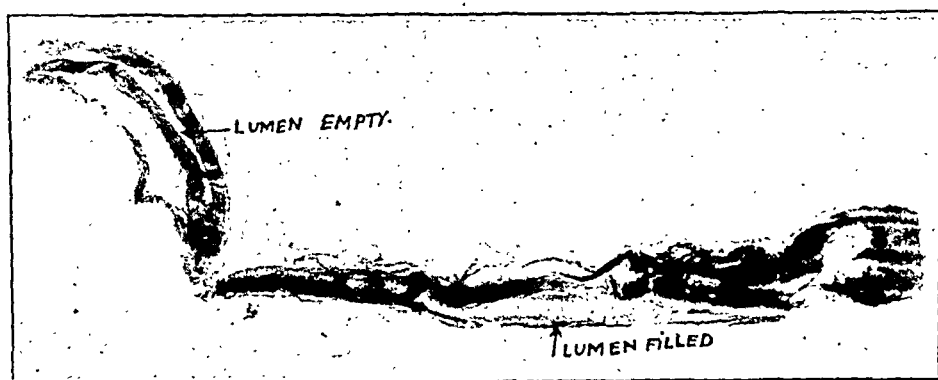


FIG. 1.—Longitudinal section of an arteriole showing the filled segment and another part empty of blood corresponding to the intersection.

An obvious analogy applies when we consider clotting in the large vessels of the trunk. On examination of these, the clots are found to be, so to speak, in segments, with serum in the intervals. (Fig. 1). When one carefully observes the peritoneal surface of the intestine postmortem or after resection, he may see that the small vessels, chiefly the venous radicals, present the interruptions corresponding to the intercoagular spaces. This appearance, due to intravascular clotting, may be found intravital in embolism or thrombosis of the mesenteric vessels.

In vitro, segmentary coagulation can be produced, but not without difficulty. Given the conditions comparable to those existing in small vessels, the blood clots usually with the expression of serum along the wall, not with the formation of intercoagular spaces. We made use of capillary glass tubes. I tested this repeatedly with normal and abnormal blood in several cases of delayed coagulability with jaundice, and in one case of hemophilia in which fibrin showed itself only nineteen minutes after the blood was drawn. Lowering or raising the temperature of one part of the tube was of no influence. In the tubes in which the blood was allowed to flow in with interspaces of air, however, there was often intercoagular lodgment of the serum. When the glass capillary tubes were filled completely with a rapidly coagulable blood, the ends then sealed with paraffin, and the tubes suspended vertically, the irregular shrinking of the fibrin gave the appearance of segmentary coagulation. (Fig. 2.)

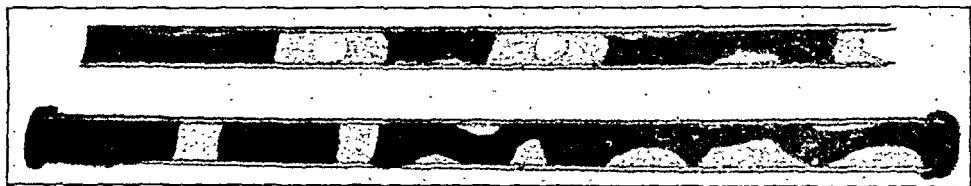


FIG. 2.—Segmentary coagulation *in vitro*.

A diligent perusal of the recent literature on ophthalmoscopy and the recognized signs of death revealed no mention of the occurrence postmortem of their segmentary appearance except in my previous studies of the subject.²

Conclusion. That segmentation of the venules and arterioles is a definite sign of death is an established fact and it should be ranked equally with the other clinical signs of death.

AURICULAR FLUTTER, WITH PERIODS OF 1:1 VENTRICULAR RESPONSE.

BY THOMAS M. McMILLAN,

AND

JOHN A. SWEENEY,

PHILADELPHIA.

(From the Department of Cardiology of the Laboratories of the Philadelphia General Hospital, Philadelphia, Pa.)

IN the vast majority of cases flutter of the auricles is associated with some degree of *A-V* block. Very rarely there may be no block, the ventricles responding to the auricles beat for beat.

² Kahn, M. H.: *Med. Rec.*, 1913, 83, 801; *Berl. klin. Wehnschr.*, 1916, 53, 1237.

As far as we can find, there are but 10 recorded instances of this mechanism. Instances of this disturbance have been reported by MacKenzie,¹ Lewis,² White and Stevens,³ Koplik,⁴ Blackford and Willius⁵ (3 cases), Smith⁶ and Hewlett.⁷ Scott⁸ recently published tracings of, and discussed, a case of this disturbance which our case resembles very closely.

A brief history of our case follows:

J. B., a white male, aged fifty-seven years, entered the medical wards of the Philadelphia General Hospital, June 10, 1923, complaining of substernal pain. At its beginning the pain had been intermittent, but about three weeks before admission it became constant, but not particularly severe. There was a history of breathlessness, fatigue on exertion and short attacks of very rapid heart action, during which the patient became very weak and extremely short of breath. These attacks came on suddenly, lasted from three to five minutes and terminated gradually. They always followed some exertion. Aside from nocturia, the rest of the history of the present illness was unimportant. The past history was negative, except for the occurrence of a penile sore ten years previously.

The examination showed a well-nourished man, who did not appear ill. In the chest were found unmistakable signs of an aortic aneurysm, which, it was thought, was the cause of the substernal pain. The heart was little, if at all enlarged; the left base measured 9.5 cm. from the midsternal line and the right 2.5 cm. At the apex could be heard a soft blowing systolic murmur. At the base in the second right interspace was heard a loud harsh systolic murmur followed by a soft blowing diastolic murmur.

The Wassermann test was positive by two antigens. The fluoroscope bore out the clinical diagnosis of aneurysm. The urinary findings were negative in the early stages of his illness, but before death showed large amounts of albumin and varieties of casts.

On admission the pulse-rate was 130. Electrocardiograms showed this to result from auricular flutter with 2:1 block.

After the studies reported in this paper had been made the flutter was easily abolished by digitalis and a normal mechanism restored. The sinus rhythm continued uninterruptedly until his death, six months later, from an acute tubular nephritis and bronchopneumonia.

Fig. 1 shows tracings from the three customary leads and an additional strip from lead II taken during vagal pressure. This latter maneuver enabled us to see the auricular waves more clearly and to determine definitely that auricular flutter was present with an auricular rate of 260 and a ventricular rate of 130.

We had obtained a history of attacks of very rapid heart action

brought on by exertion. Such an attack was induced on several occasions by having the patient bend forward and then straighten up from three to ten times. The rapid ventricular rate that resulted from this relatively trivial exercise was shown by the electrocardiograph to have resulted from the ventricles responding to every auricular impulse instead of to every second impulse of the fluttering auricle. The auricular rate was unchanged; the ventricular rate was doubled and equalled that of the auricle. The shape and duration of the *Q-R-S* complex was quite the same as

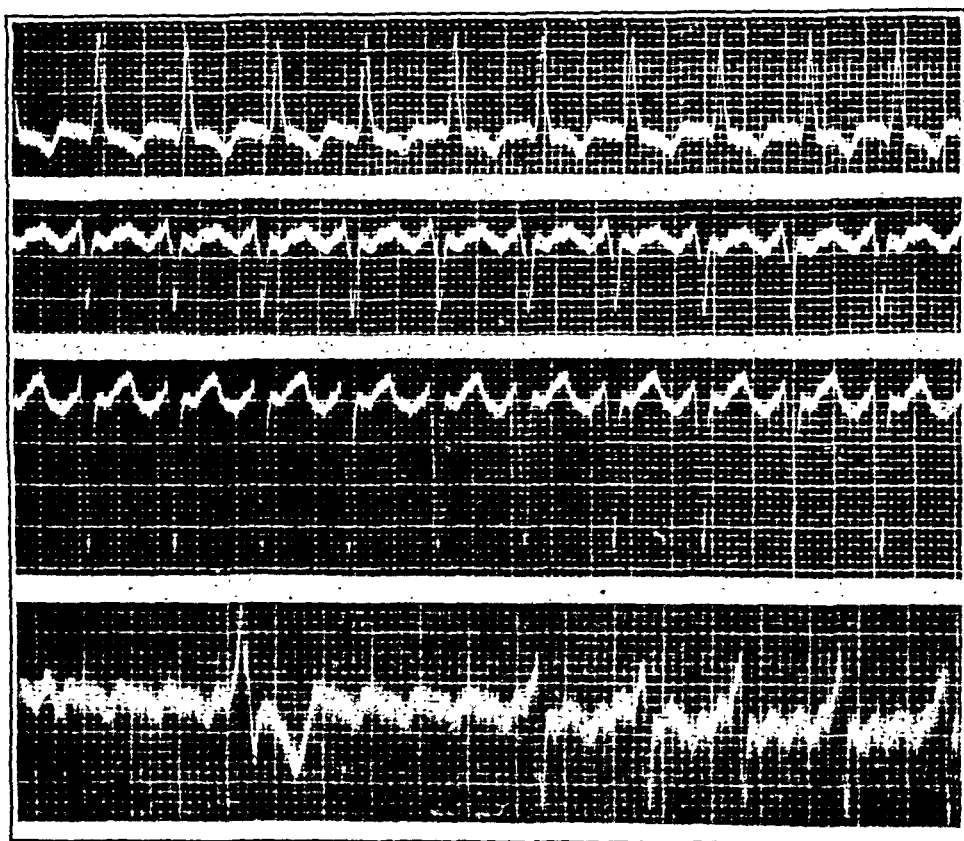


FIG. 1.—The first three strips are from the three customary leads. They show a left ventricular preponderance and auricular flutter with 2:1 block. The lowest tracing is a strip of lead II taken during the application of vagal pressure. This slowed the ventricular rate and showed more clearly the character and rate of the auricular waves. Time in one-fifth and one-twenty-fifth second.

when 2:1 block was present. Figs. 2 and 3 are electrocardiograms obtained during a paroxysm of this 1:1 conduction. These paroxysms of rapid heart action would continue unabated for perhaps three minutes. Irregularities in the ventricular responses could then be noted. In Figs. 2 and 3 it can be seen that these irregularities were due to an occasional failure of the ventricle to respond to an auricular impulse. This failure of response gradually became more pronounced until every third auricular impulse failed to be followed by a ventricular contraction. This type of action soon

gave way to the regular and constant 2:1 ventricular response present before the rapid rate set in. It can be seen in Figs. 2 and 3 that, during the transition stage from 1:1 to 2:1 conduction, the

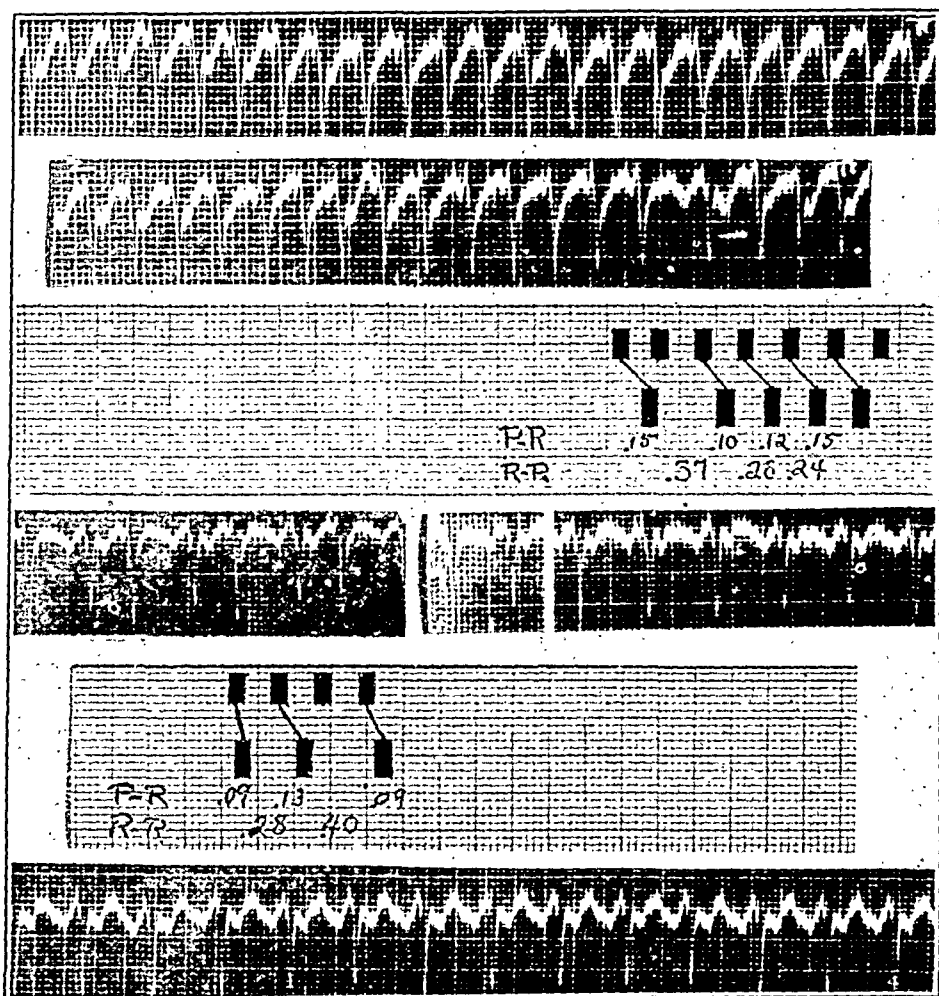


FIG. 2.—The first strip shows a paroxysm of 1:1 conduction at its height. The second strip is continuous with the first. The first irregularity in the ventricular response to appear is shown toward the right of the tracing. This irregularity is due to failure of the ventricle to respond to an auricular impulse. The third strip is a diagram to illustrate the variation of the P-R and R-R intervals in the preceding record after a failure of ventricular response. The fourth strip: Part I shows a further stage in the return to 2:1 conduction. Two successive auricular impulses cause ventricular responses; the third auricular impulse is blocked. Part II is continuous with the first part. The white line signals the beginning of vagal pressure (see text). From this point on 2:1 response is permanent. The fifth strip is a diagram to illustrate the behavior of the P-R and R-R intervals. The sixth strip is continuous with the fourth and shows a continuation of the reestablished 2:1 conduction. Time in one-fifth and one-twenty-fifth second.

actual A-V conduction time varies: after a dropped beat the next ventricular response occurs after a shorter P-R interval. Where cycles of both 1:1 and 2:1 conduction are seen the differences of A-V conduction time in these respective cycles are such that the

R - R interval of a 2:1 cycle is considerably less than twice as long as the R - R interval of a 1:1 cycle. The cause of this change in A - V conduction time is to be discussed presently.

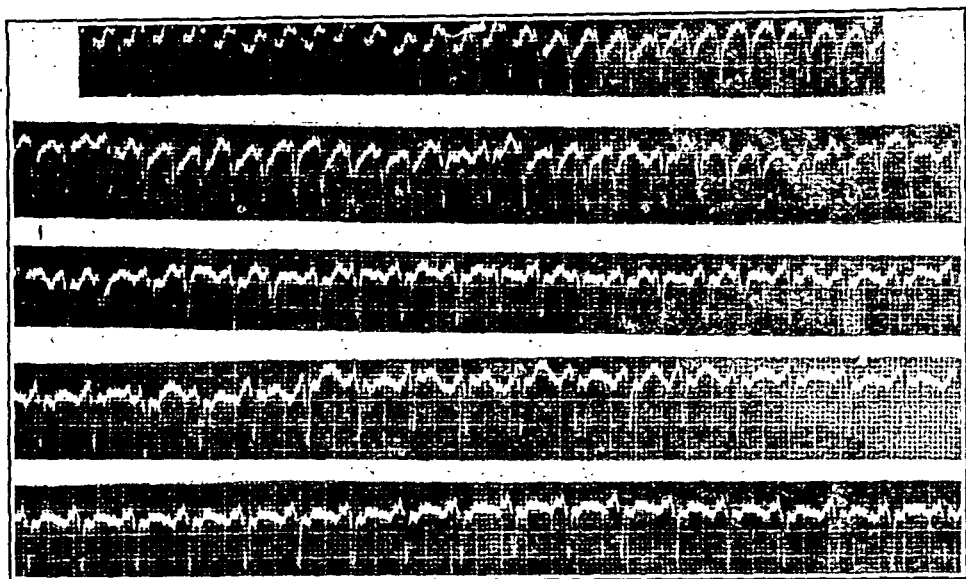


FIG. 3.—This is a continuous tracing of a short paroxysm from the beginning of 1:1 conduction to the final restoration of 2:1 response. Time in one-fifth and one-twenty-fifth second.

Discussion. *The Cause of the Change from 2:1 to 1:1 Conduction.* The factor in this case that so suddenly and profoundly modified the rate of ventricular response to auricular impulses was in all probability an alteration in the duration of the refractory period of the muscle of the A - V node. This conclusion is based on deductions made by Lewis⁹ from certain of his experiments. He believes that the evidence of these experiments, as well as certain other considerations, points to the conclusion that certain forms of heart-block are finally to be explained in terms of altered excitability of various portions of the cardiac musculature.

That actual dropped ventricular beats result from the muscle of the A - V node being in a refractory state at the time of stimulation is a generally accepted statement; but that delay in conduction results from a state of partial refractoriness was not recognized before Lewis's work. According to Lewis, excitability and conductivity are interdependent and not independent properties of heart muscle.

In studying the effects of rapid stimulation on various structures of the heart, Lewis showed that when a critical rate of stimulation was reached certain abnormalities in the cardiac response occurred. These abnormalities were: (1) A prolonged conduction time of the impulse, and (2) as the rate of stimulation was advanced somewhat, an actual failure of response. The critical rate of stimulation beyond which these abnormalities occurred varied for different portions of the

heart. In the case of the *A-V* node prolonged conduction occurred at rates of 272 to 300 per minute. When this structure was stimulated by auricular impulses at rates higher than this critical level the ventricle would respond only to every second impulse. This failure of ventricular response was in no way due to lack of excitability of the ventricular muscle, for the ventricle could be made to respond at even higher rates when the stimuli were directly applied to this structure. The site of the block was evidently the *A-V* node.

A similar phenomenon occurred in the auricle. The critical rate at which these abnormalities of conduction occurred lay, however, at a higher level.

The cause of these abnormal responses to rapid stimulation by the auricle was found by a study of the effect of vagal stimulation. Lewis showed that when prolonged conduction, or even 2:1 response, was occurring in an auricle being stimulated at a rate above the critical level, vagal stimulation would abolish both these abnormalities of conduction. His conclusions were that the 2:1 response resulted from the muscle being completely refractory at the time of each second stimulation. The state of prolonged conduction time that preceded 2:1 response resulted from the muscle being partially refractory. In finding excitable fibers under these conditions the impulse had to pursue a circuitous path, and thus prolonged the time of conduction. There was no change in the actual rate of fiber conduction. Vagal stimulation abolished these abnormalities by shortening systole and thus shortening the refractory period by increasing the time for the recovery of excitability.

In the case of the *A-V* node vagal stimulation had no such effect in abolishing delayed conduction or 2:1 response; it increased the block. Rather than believe that vagal stimulation has a fundamentally different effect on the muscle of the auricle and node, Lewis formulated the hypothesis that vagal stimulation has two effects on the muscle of these two structures. The first effect is a shortening of the length of systole. This allows recovery to begin earlier, and thus assures a quicker return of excitability. The second vagal effect is a decrease in the rate of the recovery process. In the case of the auricle the first vagal effect predominates, whereas in the *A-V* node the second effect predominates. Thus Lewis explains the differences seen in the two structures on vagal stimulation.

If we accept Lewis' explanation of these phenomena,* we can say of the case reported here that: (1) The periods of 2:1 ventricular response resulted from the muscle of the *A-V* node being completely refractory to every second auricular impulse; (2) that the periods of 1:1 response following exercise resulted from a lessening

* This explanation has been discussed by Scott (loc. cit.)

of the refractory state of the muscle or at least of some of the fibers; (3) that the prolonged *P-R* intervals seen during 1:1 conduction resulted from the impulse having to traverse a circuitous path due to the muscle of the *A-V* node being partially refractory.

As to what process caused the sudden change in the excitability of the *A-V* node in this case we can only surmise. We can only say with certainty that the change followed exertion. The effects of exercise on the heart are complex. Release of vagal tone is certainly one of the most conspicuous. According to the hypothesis of Lewis cited above, this latter reaction might bring about the periods of 1:1 conduction by speeding the rate of recovery of excitability. Considerable light could have been thrown on the relation of vagal inhibition to the onset of these paroxysms of 1:1

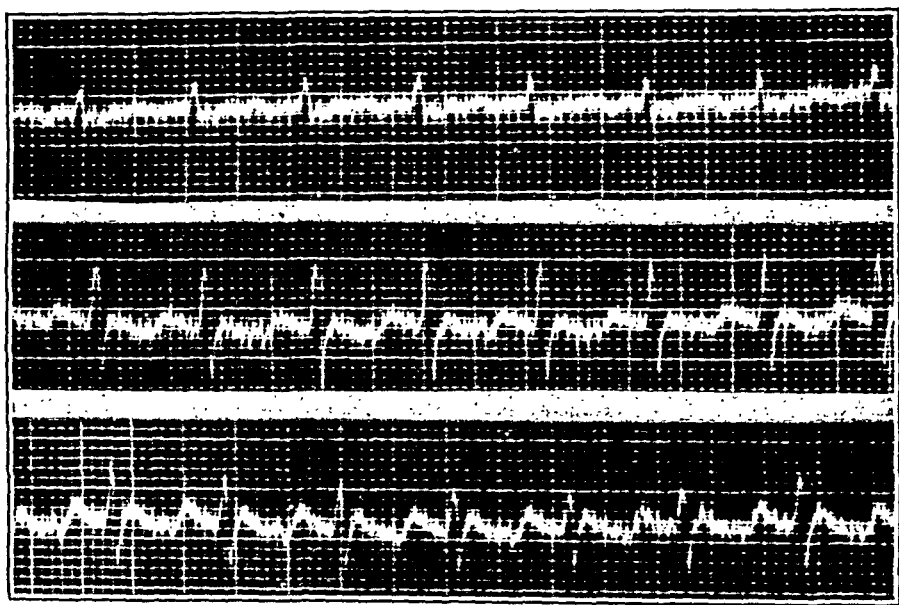


FIG. 4.—Case II. A tracing showing auricular flutter with 2:1 block. Time in one-fifth and one-twenty-fifth second.

conduction could we but have induced such a response by atropin or ended a paroxysm by vagal stimulation. We dared not make the atropin study because of the severe effects on the circulation of these paroxysms. The effect of vagal pressure, as we observed it when applied during the periods of 1:1 conduction, was to increase the degree of block. In Fig. 2 is shown the effect of vagal pressure applied while alternating cycles of 1:1 and 2:1 conduction were occurring. The spontaneous changes in conduction occurred so rapidly, however, that we do not feel that we can speak positively of this reaction.

The Circulatory Response to the Rapid Ventricular Rate. The effects of a tachycardia, such as this case exhibited, depend on many individual factors. In the case we are reporting, while 2:1 cor-

duction and a ventricular rate of 130 was present, there was little or no embarrassment. With the onset of 1:1 conduction, however, the circulatory distress became extreme. Fortunately the paroxysms were of short duration.

The Frequency of Periods of 1:1 Conduction during Auricular Flutter. The scarcity of reported cases of this mechanism would indicate that it occurs but rarely. It is our impression, however, that this disturbance occurs more frequently than the number of reported cases indicate. This impression is strengthened by our having obtained a history strongly suggestive of this disturbance in

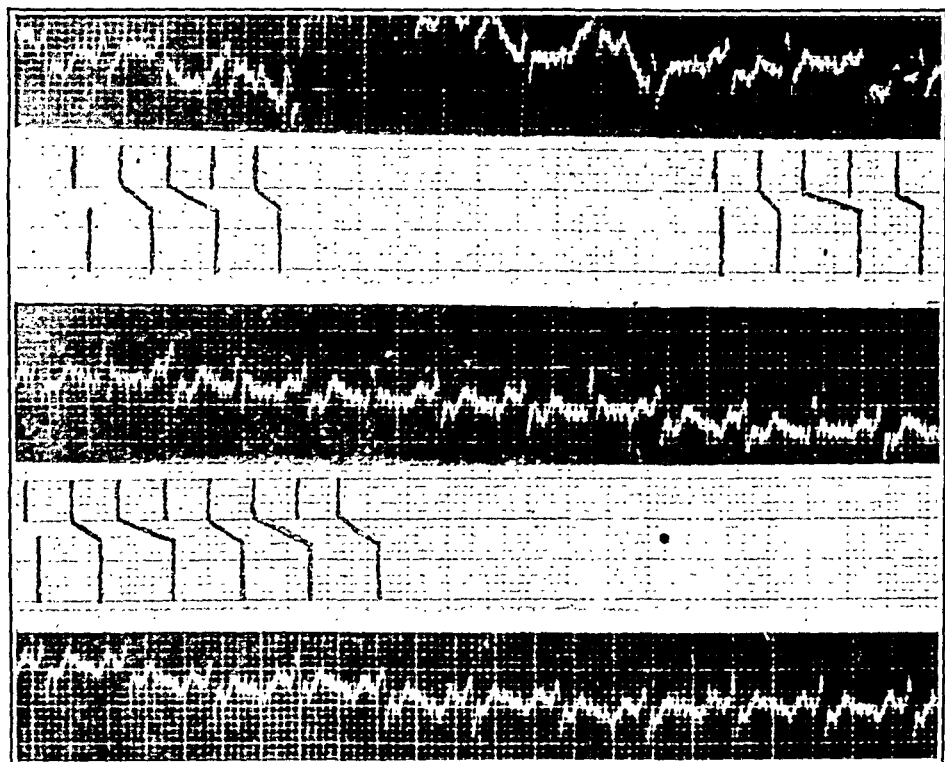


FIG. 5.—Case II. A continuous tracing of lead II taken after moderate exertion. For a time, as shown in the diagrams, the ventricle responded to two successive auricular impulses, each third auricular impulse being blocked. Time in one-fifth and one-twenty-fifth second.

several other cases of auricular flutter. Since the case reported here came to our attention, we have had but one other case of auricular flutter on which it seemed safe to attempt to induce 1:1 conduction. In this second case, hopping ten times on each foot brought on a 3:2 response for a time, that is, there were alternate cycles of 2:1 and 1:1 conduction. Figs. 4 and 5 are examples of this mechanism.

Summary. A single case of auricular flutter is reported in which the ordinarily present 2:1 block was interrupted by periods of 1:1 conduction, which lasted two to three minutes. These paroxysms

were very easily induced by relatively slight exertion. When present these paroxysms placed a serious and alarming strain on the heart.

A second case of auricular flutter is reported in which exertion brought on 1:1 conduction in alternate cycles.

It is suggested that periods of 1:1 conduction in auricular flutter are more common occurrences than the scarcity of reported cases would indicate.

BIBLIOGRAPHY.

1. MacKenzie, Sir J.: Diseases of the Heart, 3d edition, Oxford Medical Publications, London, 1913.
2. Lewis, Sir T.: Lectures on the Heart, Paul B. Hoeber, New York, 1915.
3. White, P. D., and Stevens, H. W.: Arch. Int. Med., 1916, 18, 712.
4. Koplik, H.: AM. JOUR. MED. SCI., 1917, 154, 834.
5. Blackford, J. M., and Willius, F. A.: Arch. Int. Med., 1918, 21, 147.
6. Smith, S. C.: Heart Records; Their Interpretation and Preparation, F. A. Davis Company, Philadelphia, 1923.
7. Hewlett, A. W.: Pathological Physiology of Internal Diseases, D. Appleton & Co., New York, 1923.
8. Scott, R. W.: Jour. Am. Med. Assn., 1922, 79, 1984.
9. Lewis, Sir T.: Quart. Jour. Med., 1921, 14, 339.

REVIEWS.

HANDBOOK OF SKIN DISEASES. By FREDERICK GARDINER, M.D.,
Lecturer on Skin Diseases, University of Edinburgh. Second
edition. Pp. 248; 46 figures and 12 colored plates. New York:
William Wood & Co., 1924.

THIS pocket-manual is in the quiz-compend class, and while
designed for students lacks the concise, categorical characters
that make American counterparts so valuable in a crowded curri-
culum, and which it cannot hope to replace. The illustrations are
not bad; binding, printing and quality of paper are good; but the
price of this small handbook is quite in keeping with the excessive
prices of English medical books in general. W.

THE FIRST CENTURY OF THE PHILADELPHIA COLLEGE OF PHAR-
MACY. Edited by JOSEPH W. ENGLAND. Pp. 728; illustrated.
Philadelphia: Philadelphia College of Pharmacy and Science,
1924.

THIS splendid book is a very complete history of the College
of Pharmacy in the past hundred years. It contains a most inter-
esting mass of historical data which should be of great interest to
anyone connected with the College and of interest to medical and
pharmaceutical historians. The book is beautifully prepared, very
well gotten up and is a tome which redounds to the credit of the
editor and editorial board. M.

INSULIN IN GENERAL PRACTICE. By A. CLARKE BEGG, M.D.
O.B.E., CH.B., M.B., Honorary Physician to Swansea Hospital,
London. Pp. 130; 4 illustrations. London: William Heinemann,
1924.

THIS is the third or fourth book that the reviewer has had the
opportunity of seeing which deals with specific directions to the
practitioner for the care of the diabetic, and more particularly with

the use of insulin. It is, however, the first that has come from England, therefore it is not necessarily an addition to an already overcrowded literature but rather is a book prepared for the practitioners of another country. It compares most favorably with those which have been prepared in the United States and in some respects is probably superior to any we have seen. On the whole, however, the little books on insulin therapy are very much of the same general type and are all equally good. M.

THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY IN THE WORLD WAR. Volume XI. Surgery. Part Two. Pp. 827; illustrated. Washington: Government Printing Office, 1924.

THIS third volume of the Medical Department of the United States Army in the World War which has just appeared is fully up to the standard of the two which have preceded it; indeed I might say that it is superior from the surgical standpoint though not historically as important as the other two volumes. This volume deals with empyema, maxillofacial surgery, ophthalmology in the United States and in the A. E. F., and otolaryngology in the United States and in the A. E. F. These various sections are very well presented and profusely illustrated. The colored photographs of the lungs are beautiful examples of the printer's art. The first three sections of the book are particularly commendable, the last three are hardly as complete as the first three sections. If the succeeding volumes of the history of the Medical Department in the World War are as well executed as this present volume a tremendous amount of valuable information will be available for the medical profession and for medical officers. M.

THE FOUNDATION OF HEALTH. By WILLIAM BARNARD SHARP, S.M., M.D., PH.D., Professor of Bacteriology and Preventive Medicine in the Medical Department of the University of Texas. Pp. 256; 20 illustrations. Philadelphia: Lea & Febiger, 1924.

THE *Foundation of Health* is a physiology for the layman and more particularly the lay student who wishes to know about the various bodily processes which take place in daily life. It deals largely with physiology, with an added atmosphere of anatomy and personal hygiene, the parts melded together into a complete whole which presents a most thorough and complete exposition of what the individual should know about his own body and about the care of the body. A book of this type is hard to prepare to bring it down

to the level of the non-medical reader so that he can understand and comprehend it. The author has done this so successfully that the book can be recommended to anyone who is interested, and most of us are, in the body and personal hygiene. M.

THE HUMAN TESTIS AND ITS DISEASES. By MAX THOREK, M.D., Surgeon-in-chief, American Hospital; Consulting Surgeon, Cook County Hospital, Chicago, Ill. Pp. 548; 308 illustrations. Philadelphia: J. B. Lippincott Company, 1924.

A MOST interesting book and a title that makes one hope that a true successor to Curling has appeared. One quickly perceives, however, that the author's interest centers in the endocrinology of testicular function and the subject matter relative to true pathologic conditions is woefully relegated into a minority role, frequently discharged with extensive quotations from other authors or simply sparingly treated. That the subject of hydrocele in its entirety can be dismissed with a scant 125 lines; or that vaso-epididymal anastomosis in sterility demands only 28 lines (with no mention of Hagner's work); or that epididymitis can be dismissed with an inheritance of the last four pages of this large book, shows that the volume is poorly balanced and does not represent its title. When the author writes on his special forte and simply deals with the physiological functions, normal and perverted, the book constitutes an excellent presentation of the mass of recent literature on the subject of gonadal endocrinology, which is fairly presented, carefully analyzed and judiciously passed upon, and likewise enhanced by the author's valuable work on transplantations. On this side of the subject it represents a valuable milestone in advancing medicine. R.

A RECORD OF MEASUREMENTS, WEIGHTS, AND OTHER FACTS RELATING TO MAN. THE WILLIAM RAMSEY HENDERSON TRUST REPORTS NOS. 2 AND 3. By J. F. TOCHER. Pp. 172. Edinburgh and London: Oliver and Boyd, 1924.

THIS volume constitutes the second and third of the Henderson Trust Reports, the first having been published in 1905. It consists of anthropometric observations on samples of the civil populations of Aberdeenshire, Banffshire and Kincardineshire, and a study of the chief physical characters of soldiers of Scottish nationality and a comparison with the physical characters of the insane population of Scotland. A.

MODERN METHODS OF TREATMENT. By LOGAN CLENDENING, M.D., Assistant Professor of Medicine, Lecturer on Therapeutics, Medical Department of the University of Kansas. Pp. 692; 77 illustrations. St. Louis: The C. V. Mosby Company, 1924.

THE purpose of this book, according to the author, is "to present a comprehensive statement of the best modern thought and practice upon the treatment of diseases included in the general specialty of internal medicine." "A book on treatment," he continues, "should give a method of procedure so clearly and minutely that a person who has never heard of it could do it from the description." The pages which follow admirably carry out these ideas. Approximately one-quarter of the book is devoted to instruction in the use of important drugs; unimportant ones are omitted. One-third of the work describes the application of therapeutics to particular diseases. The remainder is devoted to the consideration of special methods of treatment, such as biologic therapy, dietetics, mechanotherapy and radiotherapy. The brief chapter on psychotherapy is especially worth reading. The book will commend itself to practitioners of internal medicine, medical students, and perhaps most of all to hospital interns, who will find included in its pages excellent descriptions of practically all of the therapeutic measures practised in the medical wards of the modern hospital. A.

THE ROMANCE OF A LIVING TEMPLE: A STUDY OF THE HUMAN BODY
By FREDERICK M. ROSSITER, B.S., M.D., L.C.R.P., M.R.C.
Pp. 254. London and New York: George Sully & Co., 1924.

THE object of this work, as stated in the author's preface, is to arouse in the young a deeper interest in the study of the human body and to instil a "practical knowledge of the physical basis of happiness and morality. The teacher who can create in the young mind a love for the laws of health has accomplished a mighty work in preventive medicine. To regard the body as a temple is not vital, but to see the bearing of practical physiology and hygiene upon yourself is of the greatest importance."

To these ends Dr. Rossiter uses an extended simile of workers erecting a building, stress being laid upon the materials employed and upon the care bestowed on the welfare of the "workers," represented by the various physiological functions.

Dr. Rossiter's simplicity of style and wealth of apt illustration are especially valuable in Chapters 31 to 37 inclusive, which treat of diet. Without discussing the accuracy of all statements made, the average lay reader will probably gather from the book, as a net impression, a focussing of his attention, by means of its novel style,

upon the folly of neglecting the primary laws of health, and in this respect, as the book is eminently readable, its measure of value may be not inconsiderable. W.

GENERAL CYTOLOGY. Edited by E. V. COWDRY, formerly Professor of Anatomy at Union Medical College, Peking, China: Member of the Staff of the Rockefeller Institute for Medical Research. Pp. 754; illustrated. Chicago: University of Chicago Press, 1924.

THIS volume is the result of the combined efforts of thirteen scientists each writing of that phase of cytology most intimately related to his own field. It shares, therefore, the advantages and disadvantages inherent to this type of composite presentation. A variation of excellence is one of the disadvantages and it is evident in the present work. While most of the sections deserve the highest praise and are the most authoritative statements on their subjects today, especially perhaps those by Conklin, McClung, Cowdry and Jacobs, that on the Chemistry of Cells is so inferior as to seriously mar the value of the volume. Phrases such as on page 22—"For all practical purposes, however, the ether which we have called space and time may be referred to as Infinity and Eternity"—seem out of place in a work of this character; nor does a loose statement such as on page 48, "In its (iron's) absence hemoglobin cannot be formed and the disease known as chlorosis is the result."

The other sections, however, make the book invaluable to the worker in this field, although it is scarcely digestible by the undergraduate student. The volume is beautifully prepared and illustrated. An unimportant typographical error on page 4, and on page 367 a transformation of Archives of Internal Medicine into "Arch. Internat. de méd.," suggest the need of some revision. P.

ARTIFICIAL LIMBS: APPLIANCES FOR THE DISABLED. By DR. FLORENT MARTIN, Director of the Technical and Scientific Institute of Artificial Limb Fitting, Brussels. Geneva: International Labor Office, 1924.

THE International Labor Office publishes this volume with the desire to be of service to all persons disabled either in war or in industry. The reasons for its publication may be given in a few words. Its object is the general dissemination of information, and it is therefore not purely scientific in character. It is intended to present information to all those who for any reason are interested in artificial appliances; disabled soldiers or sailors, persons injured

in industrial accidents, institutions for insurance against accidents, invalidity, sickness, etc. It should provide anyone who wishes to obtain an artificial appliance for any given mutilation with precise data as to the conditions which should be fulfilled by any satisfactory appliance, and the best types of limb manufactured in the different countries.

After summarizing the general principles on which surgical and orthopedic treatment of amputations should be based, the author reviews the appliances at present in use, classifying them according to the type of amputation and the method of artificial limb manufacture. He draws attention to those appliances only which are of real and demonstrated practical value and has deliberately omitted experiments in limb manufacture. A brief description is given of each limb mentioned, accompanied by a sketch or photograph and a critical appreciation, so that the reader may be in a position to form an objective opinion. E.

CLINICAL ASPECTS OF THE ELECTROCARDIOGRAM. By HAROLD R. B. PARDEE, M.D., Associate in Medicine, Cornell University Medical School. Pp. 222; 56 illustrations. New York: Paul B. Hoeber, 1924.

THERE have been published recently a number of books for beginners in electrocardiography. Of these Dr. Pardee's stands out as the most interesting, since he has not hesitated to incorporate his own experience and opinions. It is not surprising, therefore, that the book has some of the faults that accompany this outstanding virtue, but they are of minor importance. The style is simple and direct and the thought clearly expressed. The discussion of the various aspects of electrocardiography is adequate for the most part to serve as an introduction to the subject. An excellent case is made out for the clinical use of the electrocardiograph. W.

DISEASES OF THE EYE. By CHARLES H. MAY, M.D., Director and Visiting Surgeon, Eye Service, Bellevue Hospital, New York. Eleventh edition. Pp. 445; 374 illustrations. New York: William Wood & Co., 1924.

THIS handbook is admirably arranged for students and practitioners, although it is not intended to replace the larger text-books of reference.

Each chapter commences with an anatomical and physiological review of that part of the eye to be discussed, which is a distinct asset in studying the different diseases of the eye and its adenexia.

The chapters on Uveitis and Disturbances of Motility have been rewritten. The size of the book has not been enlarged, though in its revision it has been brought up to date. S.

PROTOPLASMIC ACTION AND NERVOUS ACTION. By RALPH S. LILLIE, Professor of General Physiology, University of Chicago. Pp. 417; 6 illustrations. Chicago: The University of Chicago Press, 1923.

THIS is a discussion of the fundamental properties of living matter, from the physicochemical point of view. The chief distinguishing characters of organisms are growth, development and an integrative correlation of activities. The essential problem in the physiology of growth is that of the conditions of specific synthesis in protoplasm, and the problem of integration resolves itself largely into the study of the conditions under which protoplasmic processes, although spatially separated, mutually influence one another, *i. e.*, the problem of transmission. To the solution of these questions the author has made valuable contributions, one of the more recent of these being the study of chemical transmission along an iron wire immersed in nitric acid. He has been able to show in some detail the parallels between the transmission of these chemical effects in the inorganic model and the transmission of nerve impulses in living nerves. He has also devoted much time to the study of cellwalls as semipermeable membranes and the relation of their properties to anesthesia and metabolism. In this book he has brought together and reviewed his results, thus giving a collected discussion of these fundamental but intricate processes of life.

A.

ANESTHESIA IN DENTAL SURGERY. By the late THOMAS D. LUKE, M.D., F.R.C.S. (EDIN.). Edited by J. STUART ROSS, M.D., F.R.C.S. (EDIN.), Honorary Anesthetist, Edinburgh Dental Hospital, and Lecturer in Anesthetics, Edinburgh University. Fifth edition. Pp. 238; 45 illustrations. London: William Heinemann, 1924.

THE fact that this is the fifth edition is proof of the popularity of the book in Great Britain. The first chapter is a very complete history of anesthesia. The authors indicate a marked preference for general anesthetics in dental surgery, and give an excellent presentation of nitrous oxide, ethyl chloride, ether and chloroform as adapted to this field. The chapter on local anesthesia is inadequate when measured by the standards of American practice.

I.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI,
CINCINNATI, OHIO.

Exsanguination-transfusion, A New Therapeutic Measure in the Treatment of Severe Toxemias. — ROBERTSON (*Arch. Surg.*, 1924, 9, 1) as a result of his extensive experience in treating the various toxemias of children, has come to place great reliance on the operation of exsanguination-transfusion. The technic calls for replacing all, or nearly all, of the patient's blood by the blood of donors, so that the method is necessarily limited in its application to children because of the difficulty of obtaining sufficient donors for larger patients. Several donors are always prepared and at hand before the operation is started even on a child. Best results have been obtained when practically the whole of the child's blood is replaced. Blood is drawn from the donors, citrated to 0.35 per cent, and kept at body temperature until needed for injection. The child is bled from the superior longitudinal sinus in case the fontanelle is still open, otherwise from the superficial veins. When exsanguination has proceeded to the point where the pulse begins to weaken, the injection of the donors' blood is begun. Thereafter the two processes go on simultaneously. To date (March, 1924), the operation has been repeated on 501 occasions, with increasingly beneficial effects. Best results are seen in children suffering from the toxemias of severe superficial burns, erysipelas, acute septic scarlet fever, and in acute intestinal intoxication.

The Effect of Iodin in Exophthalmic Goiter. — The definite value of iodine therapy in exophthalmic goiter reported by Plummer from the Mayo Clinic in May, 1923, has since been confirmed and emphasized by PLUMMER and BOOTHBY (*Jour. Iowa Med. Soc.*, 1924, 14, 66) at the Mayo Clinic and by STARR, WALCOTT, SEGALL and MEANS (*Arch. Int.*

Med., 1924, 34, 355) at the Massachusetts General Hospital. The latter group of investigators studied a series of 25 exophthalmic goiter cases treated identically in the hospital. *Liquor iodi compositi*, U. S. P., was used uniformly, the usual dose being 15 drops daily well diluted in water and taken after meals. Twelve of the 25 patients responded to the iodine therapy with the acute iodine remission resembling the effect produced by subtotal thyroidectomy. Eight others showed remissions of a less extensive degree. Of the 5 cases treated unsuccessfully, 2 of the patients were pregnant and a third had cardiac decompensation. So if the uncomplicated goiter cases treated under iodine, 92 per cent showed marked improvement. In every case, however, where iodine was discontinued, there occurred within one or two weeks a rapid rise in metabolic rate and an increase of toxic symptoms. The important point is made that, if a patient receiving iodine is to be operated upon, the iodine therapy should not be discontinued before the operation on account of the recurrence of symptoms noted above.

The Nasal Accessory Sinuses in Cardiopathies.—Three cases, with autopsy findings, are reported by *Murphy and Ober*, *Med.*, 1924, 34, 177) in a preliminary discussion of the transmission of a careful scrutiny of the inorganic model and the transmission of vegetative endocarditis. In cases. He has also devoted much to vegetative endocarditis there were as semipermeable membranes and life, yet at autopsy one or two maxillary sinuses were seen to contain pus and to show evidence of rather long-standing infection. He advises thorough investigation of the nasal sinuses in all cases of vegetative endocarditis in the hope that no cases of sinus empyema be overlooked.

The Ex-service Man and His Lungs.—One of the most interesting developments of the war has been the large number of ex-soldiers who have been crippled as a result of infection of the lungs, the majority of cases, at least in the minds of these ex-soldiers, as a result of the inhalation in small quantities of one of the lethal gases. *Hawes* (*Jour. Am. Med. Assn.*, 1924, 83, 1490) describes his experience from a study of 1200 such cases. He divides the 1200 cases that he has seen and of which he has accurate records into groups as follows: (1) Tuberculosis, active and inactive; (2) cases wrongly diagnosed as tuberculosis; (3) gas and its complications; (4) influenza and its complications; (5) non-tuberculous pulmonary conditions. Of the first group he says tuberculosis is primarily a great diagnostic dumping-ground, and that whereas twenty-five years ago the tendency was to avoid making a diagnosis until the disease was fully fledged, now the pendulum has swung in the other direction and that in these ex-service men the tendency is to describe all symptoms referable to the chest as tuberculous; the great majority of these patients did not have active tuberculosis though many of them have the signs of an inactive lesion. As causes for the wrong diagnoses of tuberculosis he attributes the errors in part to three main divisions: (1) Failure to spend sufficient time in history taking; (2) lack of temperature and pulse records; and (3) overemphasis of the roentgen-ray findings. The causes of error apply not only to the examination of ex-service men but also to the civilian. Hawes also points out that of the 344 cases that were referred to him because of pulmonary

symptoms which were thought to be due to gas, that in only 19 or 5 per cent could he say that gas had been a factor in a subsequent tuberculous process, but on the other hand chronic bronchitis occurred in 147 of these gassed men. The diagnosis of a neurosis was the only one that could be made in 25 per cent of these gassed cases. These figures are particularly interesting because in the mind of the average physician there has developed the idea that gas has been the cause of a great number of pulmonary cripples, and this idea is even more exaggerated in the minds of the laity, whereas the physicians such as Hawes who carefully study these cases and who do come in contact with large numbers of so-called gas cases found that the gases had practically no effect whatsoever on the development of a tuberculous pulmonary process. Certainly the majority of the patients who complain of gas symptoms have the fear of gas and the effects of gas so inculcated in their minds that they attribute all types of awful results to these substances. Tuberculosis of the lung is thought to be present by many of these patients because of the more or less persistent bronchitis associated with coughing, sensation of constriction of the chest and general weakness. These patients in addition to their neurotic symptoms also have the ever present desire to receive large compensation. It has been the reviewer's good fortune to have had the opportunity of following from time to time a half a dozen men who were first seen comparatively few hours after being gassed. All these men had a widespread pulmonary lesion and were severely gassed. Gradually the pulmonary signs have cleared up, these men were intelligent officers and upon their return to civil life at once began to earn a living and have done so most successfully ever since. Of course, a small number of cases such as this is not sufficiently large from which to draw conclusions, but these men were seen when their pulmonary condition was most active and have been seen steadily ever since.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND
ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES
IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SUR-
GEON TO THE PHILADELPHIA GENERAL AND
NORTHEASTERN HOSPITALS.

Intra-abdominal Biliary Exclusion from the Intestines—Cholecystitis—Nephrostomy—A New Method.—KAPSINOW, ENGLE and HARVEY, (*Surg. Gynec. and Obst.*, 1924, 39, 62) say that the principles involved are the anastomosis of the gall-bladder to the pelvis of the right kidney and ligation and division of the common duct. Immediately after the

first stage bile can be found in the urine in varying amounts, but the animals remain at practically the preoperative weight. This method does not allow for determination of the total biliary output, but pigment studies can be made. It insures a biliary fistula free from infection and necessitating none of the inconveniences of dressings or collecting apparatus.

Mortality from Empyema in Children.—LADD and CUTLER (*Surg., Gynec. and Obst.*, 1924, 39, 429) declare that empyema in children has a moderately high mortality in their experience and in that of every other surgeon who has reported an appreciable number of cases. The mortality is highest during the first year of life. After the eighth year the mortality should be low and in the present series vanished. The next most potent factor in mortality is the type of the infective organism. *Streptococcus hemolyticus* yields the highest mortality of the common kinds of infection. Avoidance of operation before the pneumonia has resolved is a factor in the low mortality of this series. Intercostal drainage with an attempt to keep the thorax closed around the tube is the operation of choice with streptococcus infection. Rib resection with freeing of pleural adhesions to allow for expansion of the lung is the operation of choice for the vast majority of postpneumonic cases, because it gives lower mortality rates, requires fewer secondary operations and yields better permanent pulmonary function.

Subcutaneous Tenotomy of the Tendon of Achilles.—GALLAND (*Am. Jour. Surg.*, 1924, 38, 213) says that it is indisputable that the vast majority of tenotomies performed on the heel cord are followed by firm union. There are cases, however, in which the functional results are not entirely satisfactory. In a large proportion of cases, the unsatisfactory result is due to the fact that the gastrocnemius-soleus group is weak. There are some, however, in which the functional failure is due to the method employed in dividing the tendon. The author describes two distinct subcutaneous tenotomies—the oblique subcutaneous tenotomy, which is indicated in all cases of equinus, in which there is no underlying spastic condition, and second—the subcutaneous plastic lengthening of the tendon which is indicated in all spastic cases and in cases in which the equinus is extreme. The amount of lengthening that will be required can be calculated by taking one-third of the distance, which separates the heel from the floor with the foot held in moderate inversion.

Treatment of Bone and Joint Tuberculosis.—BROCKETT (*Jour. Bone and Joint Surg.*, 1924, 6, 832) state that there is necessity of a definite diagnosis based on all of the recognized methods of value. It is necessary to distinguish an early primary synovial disease, in the stage before the essential articular structures are invaded from a true articular disease in which these essential structures are involved. Methods employed in treatment are not as important as the way in which the chosen method is carried out and different methods of treatment may and should be carried out in the same case for the various methods which have been so strongly advocated, must each possess virtues. The principles of the different agencies and methods must be understood

and what may be accomplished by them, particularly the conservative ones, in order that the case be given the benefit of their influence whenever and as long as it is possible, but not after their usefulness is over.

The Dangers of Unabsorbable Sutures in Gastroenterostomy.—GILL and JONES (*Lancet*, 1924, 207, 697) believe the suture of choice is chromic or tanned gut. If a gastrojejunal ulcer develops, it should be treated surgically and not medically. Excision should be performed of the original anastomosis and the ulcer and a reconstruction should be done nearer the lesser curvature. Several authors are cited who have given up silk and thread sutures, who have had no incidence of peptic ulcer since abandonment, in favor of catgut. One author, Wright, had records of 13 cases of gastrojejunal ulceration, due to silk suture. Adams recorded the occurrence of a gastrojejunal ulcer three years after anastomies with a silk knot in the center of the ulcer.

Surgery of the Knee-joint.—ALLISON (*Surg., Gynec. and Obst.*, 1294, 39, 409) says that operations on the knee-joint, which have for their object the restoration of knee-joint function demand for success the careful handling of the tissues and especially the avoidance of injury of the joint cartilages. Operations upon the knee, which have for their object the obliteration of joint function, require a careful removal of joint cartilages. In children this is all that should be done. In certain disease processes, mostly tuberculosis, operation upon the knee offers the one sure method of cure. Ankylosis should be the objective. Especially in acute infections of the knee, operations to clean the joint cavity, or to establish drainage, hold the only promise of conservation of knee-joint function. Functional use of the lower extremity may be well carried out with a stiff strong weight-bearing knee. Functional use of the lower extremity is inhibited or lost if the knee be insecure, painful or partially functioning. The dangers that can come from an insecure knee are not insignificant. The menace that shadows the life of an individual with a tuberculous knee is very real.

Chronic Stenosis of the Duodenum.—RATKOCZI (*Am. Jour. Roentgenol.*, 1924, 12, 246) state that chronic duodenal stenoses are divided into two groups—persistent and intermittent. Causes of persistent stenoses are adhesions after laparotomy, adhesions due to tuberculosis and peritonitis and tumors of the stomach and pancreas. Causes of intermittent stenoses are movable tumors, pressure of the mesentery or the superior mesenteric artery, reflex spasm resulting from a lesion elsewhere in the gastrointestinal tract. Duodenal stenoses do not belong to diseases of great rarity. The roentgen examination is decisive. It has to ascertain whether there is an organic disease in question and whether there exists a motor disorder, both of which justify the intervention of the surgeon.

The Etiology of the Femoral Hernial Sac.—BUCKLEY (*Jour. Brit. Surg.*, 1924, 12, 60) says that the sac of a femoral hernia is a preformed sac and is not formed contemporaneously with the expulsion of a viscus. There is not sufficient proof that this preformed sac is of congenital origin. The sac is acquired as a result of properitoneal fat being herni-

ated into the thigh, through that naturally weak site in man—the crural ring. This hernia of properitoneal fat drags with it a small peritoneal sac. Anatomically a man is as much liable to a femoral hernia as a woman. The greater frequency of the condition in women is due to pregnancy and to the prolonged period of raised intra-abdominal pressure, which that condition produces. No existing theory accounts for the fact that among the comparatively few cases which occur below the age of fifteen years, female have a two to one majority.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,
NEW YORK.

Contraindications to the Use of Digitalis in Certain Types of Cardiac Insufficiency.—BOEDET and YACOEEL (*Arch. de mal. du coeur.*, 1294, 6, 335) report 3 similar cases of cardiac insufficiency having aortic involvement of different degrees, regular and slow pulse, positive blood Wassermann, and subject to attacks of angina. In each case the angina was aggravated or precipitated by digitalis therapy while intravenous injections of ouabain caused relief of symptoms. Clinical examination during the acute attacks of the angina revealed acute or subacute cardiac insufficiency, and the roentgen-ray a heart more distended than between attacks. After a course of ten to twelve intravenous injections of ouabain in $\frac{1}{4}$ -mg. doses the diameters of the heart were diminished and clinical symptoms stopped. On the contrary when digitalis alone was used the original attacks were more numerous and more severe and the roentgen-ray showed a more marked distention of the left ventricle. Ouabain augments the systolic contraction of the ventricle by increasing the tone of the ventricular muscle, and the attacks of angina cease. Digitalis on the other hand slows the heart-rate by prolonging diastole, and an overdistention of an already distended ventricle results and precipitates an attack of angina and cardiac insufficiency. In conclusion the authors state that in cases of cardiac insufficiency with overdistention of the left ventricle digitalis may be poorly tolerated. When the heart-rate is regular and slow it may be harmful and in these cases ouabain is the medication of choice. In addition to the cases mentioned there may be borderline cases with decompensation and an acceleration and irregularity of rate. Digitalis then is useful, but should be preceded by a course of ouabain so that the permanent distention of the heart in systole may be decreased, and the heart muscle prepared for digitalization.

Constipation of Civilization and its Treatment with Substances which Increase the Bulk of Feces, Particularly Normacol.—Constipation of the present day, which is a result of the machine-age with a diet of meat,

fat and milk products which satisfy the protein requirements, but yield little residue, can be corrected according to the opinion of SCHINDLER (*München. med. Wchnschr.*, 1924, 33, 1130) in two ways: (1) By substituting sport for the lack of muscular work and thus necessitating a diet higher in calories and of greater cellulose content, or (2) by adding substances to the diet which do not irritate the intestinal mucosa as do cathartics of various kinds and yet will regulate its activity. Linseed and psyllium seed are satisfactory and easy to take, but normacol made by the firm of Kahlbaum acts in the same way, but because of its greater affinity for water is much more effective. Normacol was used in 200 cases and in two forms. One form contained a trace of the extract of frangula, the other form was without it, and was called special normacol. Two teaspoonsful of the special normacol once or twice a day is the average dose. In the first weeks of treatment of this form of constipation and in cases of constipation due to proctitis or hemorrhoids the original normacol with frangula may be necessary.

The Precipitation of the Crisis in the Treatment of Pneumonia.—GARDNER MEDWIN (*Brit. Med. Jour.*, 1924, 2, 49) reports the successful treatment of pneumonia by the precipitation of crisis by means of the subcutaneous or intramuscular injection of sodium nucleinate. From extensive experience during the pandemic of influenza in 1918 and 1919 in Alexandria it was discovered that injections of sodium nucleinate would cause a marked increase in the number of white cells whether the patient had a leukopenia or not, and simultaneously there was a corresponding improvement in the patient's condition. Records of 53 cases are reported and all except 8 responded to this treatment. In addition to the injections of sodium nucleinate sodium bicarbonate was given by mouth to the cases which showed signs of acidosis. In all cases of lobar pneumonia treated with sodium nucleinate there was rapid improvement, and in every case the crisis occurred within forty-eight to sixty hours after the first injection, no matter on what day of the disease it was administered. The preparation used for intramuscular injection was a solution of sodium nucleinate put up by the Clinical Laboratories of Paris in ampules of 2 cc containing 0.05 gm. to the cubic centimeter.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Mental Health Problems in School Children.—EBAUGH (*Am. Jour. Dis. Child.*, 1924, 28, 265) indicates the absolute necessity of close coöperation between the school authorities and mental clinics. Early maladjustment always is discoverable in school, and prompt study should be productive of results, and a great aid to the individual teacher

and school. The goal of education is to produce well-balanced persons who will adjust to their environment by meeting the realities of life instead of evading personal problems, and so developing faulty habits and poor social adaptation. Character training is as important as school instruction for efficiency and health. The cases summarized in his paper show the relation of emotional life, home environment, and training to school progress, and indicate the necessity for the study of the individual child in his total reactions to the school situation. The study of such a group of children is of practical significance when we consider that the school constitutes the real health center for the child of any district and affords the best chance for routine physical and mental examination. General ignorance of the principles of correct training of the child during the preschool and school age constitutes one of the most important public-health problems. To meet this problem, a closer relationship should be established between the school and the home through the agency of the visiting teacher, specially trained nurse and the social-service worker. Definite instruction in mental hygiene in all normal schools would be of great help to the teachers in lessening the routine problems that they meet in the management of behavior disorders in their pupils. School physicians trained in mental hygiene, school neuropsychiatric clinics in association with medical clinics and observation wards will be needed in this step. The basis of this paper is a study of 50 unselected cases referred by teachers of regular schools, and these have been summarized from the viewpoint of physical, mental, psychometric and environmental findings. Corrective modifications were suggested and the therapeutic results after a period of at least one year were recorded. The school was shown to be the ideal place for the study and correction of the mal-adjustments. The treatment cannot be undertaken too early in life.

The Intravenous Use of Mercurochrome-220 Soluble in the Treatment of Pneumonia in Children.—FREEMAN and HOPPE (*Am. Jour. Dis. Child.*, 1924, 28, 310) found the intravenous use of mercurochrome of value in the treatment of pneumonias of infants and children. The results obtained by this drug were often spectacular. The course of the disease is sometimes shortened and often abruptly terminated. They report 12 cases of pneumonia occurring in infants and children who were treated by the intravenous use of mercurochrome-220 soluble. They also report the results of animal experimentation, showing that following the injection of mercurochrome the fluid squeezed from the lungs inhibits the growth of bacteria. Of the 12 cases of pneumonia 7 were bronchopneumonia and 5 were lobar pneumonia. Two patients died. In 1, death was inevitable before the drug was given. The other case, with cyanosis of unknown origin existing for several years, showed definite improvement at first, but later failed to respond to treatment. In 7 cases one injection was all that was required. Three cases required two injections and three injections were given in 2 cases. The average dose was 0.005 gm. per kilogram of body weight, using a 1 per cent solution. The authors call attention to the fact that a very marked clinical improvement usually occurs a few hours after the injection, and that this improvement sometimes occurs without any very marked change in the temperature or pulse-rate. They also observed

that these cases of pneumonia treated with mercurochrome ran a much shorter course than cases of pneumonia of the same severity when this drug was not used. The systemic reaction in children is mild.

The Effect of the Routine Administration of Cod-liver Oil on the Development of Rickets in the Breast-fed.—DE BUYS and VON MEYSENBURG (*Am. Jour. Dis. Child.*, 1924, 28, 329) based their studies on cranial bosses, costal beading, epiphyseal enlargement, flaring ribs and craniotabes. The cranial bosses was the most frequent symptom recorded. Costal beading, epiphyseal enlargement, flaring ribs, and craniotabes followed in the order named. These symptoms developed in spite of the use of an emulsion of pure Norwegian cod-liver oil in doses of one-half teaspoonful three times a day. The average intensity of each of these clinical symptoms was greater than in a former study where no cod-liver oil was administered, with the exception of epiphyseal enlargement and costal beading. In these two the average intensity was less in this study. All the symptoms began earlier in this study than in the previous one. During the first three months of the study there were eighty-nine hours less of actual sunshine and an average of 8.3 per cent less possible sunshine per month than in the same period in the previous study. The meteorological summary for the period of this study showed the percentage of possible sunshine to be 2 degrees above the normal average. It was 1.9 degree less than for the period of the previous study. The precipitation for the period of this study was 6.28 inches above the normal and 10.91 inches more than the precipitation for the period of the previous study. The atmospheric pressure temperature and humidity were about the same as for the previous study. The seasonal peak for the combined symptoms was noted in the month of July, the greatest height being July 26. The seasonal peak for this study differed from the peak of the previous study which occurred in the month of March. During the months of July and August the percentage of possible sunshine was at its minimum for the period of this study. The precipitation during this month was more than that for any two consecutive months in the study. The increase in the precipitation for July, 1923, over July, 1922, was greater than the increase of precipitation for March, 1922, over March, 1923. The total hours of actual sunshine for the period of this study was 116.8 less than for the period of the previous study. Considering rickets from the standpoint of clinical symptoms, the disease was beneficially affected by the routine use of cod-liver oil in spite of the adverse meteorological conditions. Considered from the standpoint of all clinical symptoms sunshine and precipitation seemed to have an influence on the severity of rickets even in the presence of the administration of cod-liver oil.

Clinical Studies of Some Diseases of the Blood in Children with Illustrative Cases.—GRIFFITH (*Arch. Pediat.*, 1924, 41, 511) reports a number of cases and he feels that the blood-picture in chlorosis is of very frequent occurrence in infancy and childhood, and that such cases should be properly designated as chlorosis. The administration of iron, without any other treatment, is often of striking benefit in these cases and in simple anemia. In diseases of the blood in general, especially in childhood, the symptoms appear to be to a certain extent inter-

changeable. Without an examination of the blood a diagnosis is more likely to be mistaken than correct, and even with it a certain diagnosis cannot be based upon any one hematological feature. This is especially true of alteration in the character of the red cells, any excess either of lymphocytes or myelocytes, a high-color index or a low-color index. There appears to exist no definite relationship between the degree of alteration of the blood and that of the size of the lymphatic glands and the spleen. Variations in the blood-picture occur not only between different cases, making the differentiation of the disease present difficult, but from time to time impossible in the same case. Only careful and often repeated examinations of the blood and of the symptoms in general insure the arrival at the correct diagnosis.

A Clinical Study of Lactic Acid Milk as a Routine Feeding for Sick and Healthy Infants.—FIELD (*Arch. Pediat.*, 1924, 41, 541) claims that lactic acid milk is better for artificially fed infants than sweet milk because the protein in acid milk is precipitated as a fine flocculent curd and remains so in the stomach until the process of digestion has broken it down. The boiling of raw milk partially accomplishes the same thing but also partially destroys the vitamins. An extremely important factor in selecting a food for young infants is its "buffer" or acid binding qualities. Lactic acid milk is similar in this respect to breast milk, the pH of the gastric contents at the height of digestion of a group of infants fed on whole lactic acid milk having been found to be 3.71, while the average hydrogen-ion concentration of the stomach contents of the same group fed on breast milk was 3.75, which is probably about the optimum concentration for gastric digestion in infants under one year. In sick infants it has been shown that the actual concentration of hydrogen ions in the gastric contents averaged only one-tenth as much as that for normal infants receiving the same food, which was breast milk. It seems, therefore, rational to avoid sweet milk in feeding sick infants for thereby we diminish gastric acidity. The acid of the gastric contents when present in sufficient amounts permits peptic digestion of proteids, influences gastric mobility, and has a very definite antiseptic action. The acidity of the gastric contents is known to regulate in some measure the pyloric reflex, and acid in the gastrointestinal tract stimulates the flow of pancreatic juice, bile and intestinal secretions, and results in distinctly better absorption of all the food elements. A third reason why lactic acid milk is better than sweet milk for feeding infants is that it is practically sterile even under the most adverse conditions, or rather under the most favorable conditions for bacterial growth. In lactic acid milk there is a maximum of food value with a minimum of bulk, which in many cases is of distinct value.

Medical Aspects of Acute Appendicitis in Children.—HOWLAND (*Jour. Am. Med. Assn.*, 1924, 83, 961) says that there is justification for dreading this disease in the very young because the attacks are usually severe. Mild attacks, comparable to those encountered in later life, are distinctly rare. General peritonitis may intervene as early as the second or third day. It is not proper to conclude that this is the rule. Many patients have lived as long as would an adult, and the process has remained localized for days and sometimes even for weeks.

Howland agrees with Drachter that the problem of appendicitis in the young child is one of diagnosis, and that if operation is performed before there is a general peritonitis or pocketing of pus in numerous places, the mortality of appendicitis should be no greater but should be even less than it is with the adult.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY AT THE SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA.

The Treatment of Syphilis from an Experimental Point of View.—This article by BROWN and PEARCE (*Ann. Clin. Med.*, 1924, 3, 1), a summary from the experience of two of the most profound students of experimental syphilis, should be read in full by all who are called upon to deal with the difficult and perplexing issues of modern syphilotherapeutics. It is only possible in an abstract to single out a few specially effective statements from a text which maintains a rare plane of insight and breadth of knowledge of the problems of the disease. The authors, reviewing the past decade in the treatment of syphilis, conclude that it cannot be said that any considerable progress has been made in the treatment of syphilis in the last few years. The noteworthy improvements have been mainly in the technic of application of known remedies. Experience has shown that it is not sufficient to regard syphilis merely as a spirochetal infection to be attacked by the use of the most vigorous parasitocidal measures that the patient will endure. The treatment of syphilis is something more than this. It is in a sense a combination of applied pathology and pharmacology, in that the selection and use of any therapeutic measure must be determined by the fitness of such a measure to meet the needs of a given situation. Not only must one know syphilis in all its manifestations, but there is also need for an intimate knowledge of the human economy; for after all we do not treat the spirochete or even the disease, but we treat the patient, and the resources of the patient are destined to become more and more important. Among many orienting facts which must be kept in mind, we should remember that syphilis begins insidiously and that the invading organism is widely distributed before any clinical manifestations of the disease appear. The action of therapeutic agents has been and is but imperfectly understood. Innumerable estimations of trypanocidal and spirocheticidal action and of toxicity have been made, together with exhaustive studies of absorption, elimination and distribution. But nowhere is there to be found a comprehensive report of the biologic action of even such substances as arsphenamin and neoarsphenamin. During the early stages of acquired syphilis our efforts may be concentrated on the destruction of parasites, but once a characteristic lesion has developed it is useless to try to prevent a systemic distribution

of the organisms. It is, however, still possible to prevent the localization and growth of spirochetes in inaccessible foci and to prevent the development of lesions which afford more or less protection against the actions of spirochetal agents (that is, fibrosis and endarteritis obliterans). In very early cases the spirillicidal action of the drugs is therefore most important. The effect proceeds almost like a test-tube reaction. Yet even in the earliest cases some of the spirochetes may be inaccessible. Hence other things being equal, penetrating power as well as mere spirillicidal action must be considered among the qualities required of the drug used. The ability of the selected drug to cause resolution of lesions (healing) with resultant exposure of the organisms to its effects, must also be considered. Wide differences exist between the interrelations of these qualities in different drugs now in use. Some are parasiticidal in the blood stream but ineffective in tissue because they cannot penetrate it. Others, weakly spirillicidal, are more effective in spite of this deficiency, because of their increased penetrating power. In the advanced stages of syphilis, the hope of effecting a complete sterilization is greatly diminished by the changes that have occurred in the host. The penetrating power of the agents used therefore becomes the more important as the foci become more difficult of access. In dealing with the general immunologic problems of the disease, it should be remembered that all therapeutic agents that cause an abrupt cessation of the reaction on the part of the patient to his disease, as indicated by a rapid resolution of lesions, but which fail to destroy all the infecting organisms, operate to the disadvantage of the patient and predispose to the subsequent occurrence of more severe manifestations. In part this effect is attributable merely to the removal of the stimulus to reaction resulting from actual destruction or temporary suspension of the activity of the spirochetes. In other instances however, there is definite and more or less persistent reduction of the effectiveness of the reaction due to the effect of the drug on the patient. Moreover in cases of this kind, the earlier the treatment is undertaken the more serious are the consequences of failure on account of interference with immunologic reactions. It appears from the observations of Chesney and Kemp that permitting the immunologic reactions to develop to their full force leaves the animal after subsequent sterilizing treatment, immune or at least refractory to reinfection, although no remnant of the old infection can be demonstrated to explain the immunity. Moreover, there are remarkable differences in the character of the disease which can be produced by the use of a given procedure at different seasons of the year or in different years. It has been shown, too (Pearce) that iodids, known to be without spirillicidal effect, are able when used alone, to modify in a favorable manner, the course of experimental syphilis. Facts such as these indicate very clearly that the ability to combat a syphilitic infection is an inherent constitutional trait. It is not, however, a fixed property, but may increase or diminish with age, with season, climate and meteorologic conditions, and with changes in the physical condition of the animal. The condition of the endocrine mechanism and changes in this group of structures and in the lymphatic system are especially instrumental in determining the course of an infection. It has been found that the removal of a part or

the whole of such an organ as the thyroid will produce a profound alteration in the character and efficiency of the response of such animals to syphilitic infection. The mass relations of various organs of the body at various seasons and under varying conditions of sunlight can be correlated with change in the resistance of these same animals to syphilitic infection.

Treatment Results in Early Syphilis.—MUTSCHLER (*Arch. f. Dermat. u. Syph.*, 1924, 147, 105) reports the results of three years' observation of 55 cases of primary syphilis, 21 of them Wassermann negative on the blood and of from three to four weeks duration, and 31 with positive blood Wassermann reactions and a duration of four to ten weeks. The treatment used consisted of 10 to 12 injections per course of arsphenamin or silver arsphenamin, alternating or combined with calomel, novasurol or gray oil. Two such courses were given in the more advanced cases one course only in many of the earlier cases. The results were checked by spinal fluid and blood Wassermann examinations, physical examination with emphasis on lymphadenitis, etc. It is estimated that in the seronegative group, 100 per cent of cures have been obtained. In the seropositive group, the relapses aggregate 50 per cent in those treated with only one course, and no relapses in those receiving two courses. It should be noted that the individual courses are considerably more intensive than those customary in this country. Mutschler cited Silberstein who reported from Schlotz's Clinic 80 per cent of cures in a long period of observation of the very early cases, this result being obtained with one intensive course.

The Problem of Arsphenamin Resistant Syphilis.—SILBERSTEIN (*Arch. f. Dermat. u. Syph.*, 1924, 147, 116) discusses on the basis of the experience of Scholtz's Clinic, covering a period from 1911 to the present time, whether or not there is developing an arsphenamin resistant syphilis. Silberstein cites the experience and impressions of a number of observers in support of the belief that there is developing a distinctly arsphenamin resistant type even of early syphilis, which requires longer and more frequently repeated courses, which in spite of their increasing intensity fail to produce the results obtainable with the drug in the first years of the past decade. He directs attention also to the growing volume of reports on arsphenamin resistant syphilis in the literature. He constructs from the experience of the Scholtz Clinic a very interesting table, evidencing the increasing resistance of early syphilis to methods of treatment which were effective in the earlier days, as follows: The Wassermann reaction became negative in the years 1911-1916: In 236 patients after one series of treatments, 198 times or 85 per cent; in the remaining 38 patients after 2 series, 30 times or 78 per cent.; in the remaining 8 patients after 3 to 4 series, 8 times or 33 per cent. The Wassermann reaction became negative in the years 1921-1922: In 60 patients after 1 series, 14 times or 23 per cent; in the remaining 46 patients after 2 series, 25 times or 54 per cent; in the remaining 21 patients after 3 to 4 series, 7 times or 33 per cent. It was rare, the author states, to observe an irreversible positive before the war, yet

since the war such cases aggregate 23 per cent of the total treated. After considering the various possibilities which may explain this very obvious difference in the treatability of the disease during the past decade, the author concludes that a difference in the resistance of current strains, so to speak, of *Spirochæta pallida* to arsenicals, actually exists, and that the necessity for massive early treatment and varied methods becomes therefore the more urgent as time elapses. Ehrlich, in one of his discussions of chemotherapeutic problems as applied to syphilis, indeed foreshadowed this very possibility.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

Cesarean Section for Occlusion of the Vagina and Calculus.—FRETZ (*Brit. Med. Jour.*, August 23, 1924) reports the case of an East Indian woman who had been in unsuccessful labor and was brought to a hospital. On examination there was absolute occlusion of the upper two-thirds of the vagina by a dense fibrous band. The cervix could not be found. On the anterior vaginal wall in front of the adhesion was a hard calcareous mass which, on removal, proved to be a phosphatic stone. After its removal urine trickled into the vagina, showing the presence of a fistula. It is thought that the fibrous obstruction was caused by the chronic irritation from the fistula. The patient was successfully delivered by Cesarean section and did well until the twelfth day. She then became maniacal and died of exhaustion on the sixteenth day. The child survived.

The Sheppard-Towner Act.—In the *Journal of the American Medical Association*, September 13, 1924, is published an editorial calling attention to the recent statement of work accomplished by the Government under this Act. In 1922, 43 states coöperated, 41 in 1923, 40 in 1924. Analyzing all claims made for the Act, there were four, of which the first three amount practically to nothing, as they state that the activities of states and local communities have been increased, and that the quality of work done for mothers and babies has improved. It did not require the Sheppard-Towner Act to accomplish this, for the profession had been working steadily for this purpose for a number of years with excellent results. The fourth claim for accomplishment is that state appropriations have increased with the passage of the Act. It must be remembered that under the Act states have been forced to appropriate money and that such appropriation does not represent a voluntary and enthusiastic accomplishment. If the advocates of this measure would justify the Bill, they must submit exact figures indicating that the maternal and infant death-rates have been appreciably lowered in those states which have coöperated with the Federal Government, and that the rates of expenditure are much lower than those obtaining

before this meddlesome legislation became effective, and that such rates are lower than those in states which have not coöperated. The defendants of the Act cannot ignore the tendency to increased activity and improvement in results which had been begun before the passage of the Act.

The Relation of Venereal Disease to Childbirth.—SCHUMANN (*Am. Jour. Obst.*, September, 1924) has examined 150 private cases by taking a smear from the cervix, with one positive result, and that a doubtful one not confirmed by subsequent examination. He believes that gonorrhea is much less common in pregnant women than is often stated. In cases of sterility this infection is a most important element and should such a patient conceive, abortion and pelvic inflammation frequently follow. He draws attention to the studies of Curtis showing that the tube is not the focus for chronic gonorrheal infection in the majority of cases. Gonorrhea is a widespread and pernicious agent in producing tubal pregnancy. Where this disease complicates pregnancy, vigorous manipulations should be avoided, the entire vagina and cervix should be gently coated once each week with 20 per cent argyrol solution and the patient should be instructed to fill the vagina with 10 per cent argyrol solution daily, using from 2 to 4 ounces, given by a soft rubber bulb syringe and held in place twenty minutes by closing the labia with the fingers. Chronic endocervicitis requires treatment when it produces a profuse irritating discharge, equal parts of sodium bicarbonate and Fuller's earth, placed in the vagina and retained forty-eight hours by cotton tampon, will improve the condition. At labor the birth canal should be flushed with 10 per cent argyrol solution. The solution should be allowed to remain until expelled by labor contractions. It is of great importance that the patient be not wounded by applications, and early interference in labor is to be avoided. General septic infection may be readily induced by unskilful manipulations. He calls attention to granuloma inguinale as not infrequent and occasionally complicating pregnancy. The fact that the external genital organs become the site of highly proliferous masses with foul discharge, makes vaginal delivery impossible. The treatment of the condition during pregnancy is unsuccessful and delivery by Cesarean section so soon as the child is viable, is indicated. In studying the effect produced by syphilis upon parturition, 48.4 per cent of syphilitic women gave birth to living and healthy children who gave no evidence of infection. The writer's study of the subject leads him to believe that syphilitic pregnant women, without treatment, will give birth to living and healthy children showing no evidence of syphilis in about one-half of the cases; about one-third produce syphilitic children either living or dead, 10 per cent of the whole number observed. In the remaining cases it is impossible to clearly recognize the presence or absence of syphilis. This and similar observations would lead to the belief that syphilis is not increasing throughout the world. Colles' law is still recognized and parental infection of the ovum is acknowledged. Profita's law which holds that syphilitic women may give birth to a child that is free from this disease and that never presents any manifestations of it, is also true. The general belief of the writer's study is that the steady increase of prenatal care and early recognition of disease in pregnant patients, with active and persistent treatment, is improving this condition very materially.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, MEDICAL SCHOOL, UNIVERSITY
OF PENNSYLVANIA, PHILADELPHIA.

Significance of Hematuria.—In a brief clinical study of 821 consecutive cases of hematuria, in all of which blood was grossly visible, MACKENZIE (*Surg., Gynec. and Obst.*, 1924, 39, 155) reminds us that the presence of macroscopical blood in the urine can be due to a great variety of causes, and generally signifies some serious pathological condition of the urinary tract. It is not a clinical entity which requires treatment but a symptom which demands investigation. The importance of hematuria and the necessity of determining its cause must be recognized by every physician and should be carefully impressed upon each patient suffering from urinary hemorrhage. Notwithstanding all that has been said and written on this subject, there is still a tendency for the medical profession to regard this condition lightly, to treat it without a diagnosis, and to consider a cessation of bleeding as an indication of cure. This is largely due to the fact that hematuria is usually intermittent in character. During the free interval, while the patient is apparently in perfect health, it is not surprising that both patient and physician should minimize the importance of this danger signal. It is at this time, while there is yet a probability of cure, that the best opportunity for investigation and diagnosis is afforded. An analysis of the 821 cases in this series shows that in 192 cases the hemorrhage was due to calculi, 113 to tumors, 88 to renal tuberculosis, and 143 to surgical infections of the ureters and kidneys; or, excluding the urethra, 536 cases out of 761, that is more than 70 per cent were caused by calculi, tuberculosis, cancer or surgical lesions of the kidney; while the other 30 per cent most certainly required investigation. The great importance of subjecting these patients to a careful and thorough examination is at once apparent. With the present day methods of diagnosis the origin and cause of urinary hemorrhage can be ascertained in a very large percentage of cases.

Operative Results in Cervical Cancer.—The Hunterian Lecture delivered by FORSDIKE (*Brit. Med. Jour.*, 1924, 2, 94) before the Royal College of Surgeons in 1924 was devoted to the important subject of cancer of the uterine cervix. He reminded his audience that the operative treatment of cancer of the cervix had undergone great changes in the last twenty-five years—local excision of the disease by knife or cautery, supravaginal amputation of the cervix, vaginal hysterectomy, and last of all, the radical abdominal operation. The limits of this last

operation vary with the individual surgeon, from panhysterectomy with excision of as much parametrial and vaginal tissue as possible, to resection of bladder, ureters, bowel and more or less of the pelvic fascia glands. The mortality in the more extensive operations is as high as 70 per cent and probably is rarely below 30 per cent, the average for all cases is 20 per cent and for early cases 6 per cent. The radical operation has been widely practised for twenty years and for early cases it has general support, but there is an increasing number of surgeons who question the wisdom of applying this operation to cancer which has clinically extended into the pericervical tissues, for the results are deplorable and of those who survive the operation less than 10 per cent are alive a year later. All surgeons admit that the results warrant operation in the early cases, while in the advanced cases no surgery should be done, but it is the borderline group where opinions differ markedly. Forsdike has records of 50 borderline cases treated by the radical operation in which the parametria were infiltrated by the growth, many of which came under his observation for treatment of the recurrence of the growth. The most striking feature of this series is the large number of early recurrences and the consequent relief was so transient as to be negligible. Of the 50 cases, 10 are living and 40 are dead. Of the 10 alive, 6 remain well over periods of five and a half, four and a half, four, four, three and a half, and three years, 2 remain well between one and two years, 2 are alive with recurrence under twelve months. Thus the high mortality, rapid recurrence and poor end-results cast grave doubt upon the wisdom of radical operation in this group since there are ample reports from various countries which show that the results from radium far surpass those from operation in such cases.

Treatment of Uterine Fibroids.—In his discourse upon the treatment of the various types of uterine fibroids CUTHBERT LOCKYER (*Brit. Med. Jour.*, 1924, 1, 1037) of London, who is certainly well qualified to speak states that he regards deep myomectomy, which is being revived; as involving somewhat greater risk than a supravaginal amputation, but this additional risk should be ignored if there is a chance of subsequent childbearing. When hysterectomy is indicated there is always a discussion as to whether the operation should be a total or subtotal hysterectomy and there are many good men supporting each side of the question. Lockyer is very broad-minded in his observations and believes that there are indications for both types of operation although if he had to confine himself to one or the other he would become a "totalist." It is not difficult to understand his choice because he has performed 195 total hysterectomies with 3 deaths, a mortality of 1.54 per cent, while in his series of supravaginal amputations numbering 284 cases there were 5 deaths, a mortality of 1.76 per cent. It is extremely doubtful however whether the great majority of surgeons could keep their mortality as low as this in either type of operation, especially the total operation. As regards morbidity, he states that simple cases run as smoothly after the total as after the subtotal operation and purulent cases do better with the vaginal drainage afforded by the total operation than without, but nevertheless these considerations do not justify the abolition of the subtotal operation since it is easier and quicker and may

be justifiable where the longer, more tedious and bloody procedure would not. In regard to the question of ovarian conservation, Lockyer believes that it is better to conserve one or both ovaries, if healthy, no matter what the age of the patient may be, thus he is opposed to the frequently heard statement that it is better to remove the ovaries if the patient is beyond forty years of age. In conclusion he states that in 55 per cent of all fibroids, no treatment whatever is needed. In the remaining 45 per cent, 35 per cent require removal by some type of surgical operation, leaving 10 per cent to be dealt with by radium. This is equivalent to stating that the field of operation is from three to four times as great as that for radiotherapy.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO; TORONTO, CANADA.

AND

DE WAYNE G. RICHEY, B.S., M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY, UNIVERSITY OF PITTSBURGH; PITTSBURGH, PA.

Properties of Purified Dick Scarlatinal Toxin.—"The Dick scarlatinal toxin is the filtrate from the growth in broth of certain streptococci isolated from the throats of scarlet fever cases, as has been shown by the Dicks, Dochez and Sherman." The toxic substance is produced in the largest quantities after the addition of considerable amounts of horse blood. HUNTOON (*Proc. Soc. Exper. Biol. and Med.*, 1924, 21, 513) found, after numerous investigations, that the best toxin was produced by seven-day growths; that the toxic substance is not of the nature of a globulin, but is precipitated with the higher albumin fractions; that it is a protein which is destroyed or inactivated by trypsin, and by heat (90° for one hour); that its tendency to come down in a narrow range of ammonium sulphate precipitation renders a high degree of purification possible; and that the material is neutralized by convalescent serum, but is not neutralized by normal horse serum or by the serum of horses immunized against the scarlet fever streptococcus in the ordinary manner (non-toxic substances).

Kidney Changes in Pyloric Obstruction.—ZEMAN, FRIEDMAN and MANN (*Proc. Soc. Exper. Biol. and Med.*, 1924, 21, 179) discovered, in the routine microscopical examination of autopsy material, almost identical kidney changes in 4 cases of pyloric obstruction. Two of the 4 cases exhibited, clinically, typical tetany. The renal changes consisted in degeneration of cells lining the spiral and terminal straight portions of the first convoluted tubules. In many sections these cells were necrotic and infiltrated by granules staining dark blue with hematoxylin, which merged into larger masses, entirely blocking lumina of tubules. The authors interpreted the blue staining granules as calcium

salts. The renal changes described in these cases were very similar to those noted in mercuric chlorid poisoning. The authors cannot consider these changes as evidences of nephritis, inasmuch as they were entirely degenerative in nature, being best designated by the term toxic degenerative nephrosis. Similar cases have been reported, recently, by Brown, Hartman, Eusterman and Rowntree, who attributed the presence of calcium in the kidneys to the fact that the patients had received calcium by mouth. The authors cannot subscribe to this view, believing that the primary factor is pyloric or high duodenal obstruction in association with repeated vomiting, to which the tetany and kidney changes appear to be secondary. They are unable to explain satisfactorily at present the mechanism leading to the kidney damage. Sections of the stomach and other organs in their series showed no deposit of calcium such as occurs in metastatic calcification where the amount of circulating calcium is increased.

Certain Pathological Tissue Changes in Thyroidectomized Sheep.—Of 10 lambs that were thyroidectomized early in life by GOLDBERG and SIMPSON (*Proc. Soc. Exper. Biol. and Med.*, 1924, 21, 567), 5 showed marked lesions. These consisted of subcutaneous and subserous edema with, in most cases, ascites and hydrothorax. The kidneys showed parenchymatous nephritis. The most striking changes occurred in the aorta and pulmonary arteries, which exhibited hyaline degeneration and calcification of the media in the form of plaques. There was a striking absence of fatty degeneration in any of the vessels. The controls did not show any of these tissue changes. The observations extended over a period varying from eight months to two and a half years after the removal of the thyroids. The authors believe that the arteriosclerosis can be explained on a chemical basis, perhaps due to senile changes occurring early in life as a result of complete thyroidectomy.

The Effect of Digestive Juices on the Potency of Botulinus Toxin.—“It is a general rule that the true toxins derived from culture of pathogenic microorganisms must be introduced parenterally if they are to act on the animal organism. When given by mouth, even in very large amounts, they tend to be harmless. The failure of the toxins to act under these circumstances is ordinarily ascribed to the fact that they are subject to destruction by the digestive juices. *Botulinus* toxin, however, presents a notable exception to the rule just mentioned.” After a number of experiments on mice, BRONFENBRENNER and SCHLESINGER (*Jour. Exper. Med.*, 1924, 39, 509) found that *botulinus* toxin resists a degree of acidity equivalent to that of the stomach even when exposed thereto for twenty-four hours at 37° C. The toxin was less resistant to alkali, however, as shown by the fact that in a medium of weakly alkaline reaction its potency was reduced to less than one-tenth in twenty-four hours. It was unaffected by peptic or tryptic digestion. “Because of its instability in mildly alkaline solutions and resistance to acid, there is reason to believe that the toxin is in the main absorbed from the upper portion of the digestive tract; that is to say, from the stomach and upper duodenum.”

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

Life Tables for the Population of New York State According to Nativity.—DEPORTE (*Am. Jour. Hyg.*, 1924, 4, 302) studied life tables for white males, aged twenty years and over, of the population of the state of New York with reference to native-born of native parentage, native-born of foreign or mixed parentage and foreign-born, based on the average number of deaths in the years 1909, 1910, 1911, as given in the U. S. Mortality Reports, and the population, as given in the U. S. Census Report, 1910. He states in one of his several conclusions that conditions are more favorable among foreign-born than among native-born of foreign and mixed parentage. This, he believes, is due partly to natural selection, artificial selections and occupational differences, but mainly to the unwise social pressure toward superficial Americanization, as a result of which a large fraction of the native-born of foreign parentage become strangers to their parents, grow up without home influences, forsaking the culture and traditions of their people, and finding nothing in the life of the street to take their place. The reason cannot be the biological weakness of a blend, since the native-born of the first generation are in most cases products of the same racial strain. This opinion finds support in the fact that in Minnesota, where the population is still largely rural, where the foreign-born and the native-born have been from the beginning of settlement of the same Teutonic stock—English, German, Scandinavian, where the neighbors of a native-born person were very likely people of the same or similar strain, and of comparatively recent origin, where the old-home traditions of the peoples had not been held in contempt, and where therefore Americanization was a process of addition and not of total rejection of everything "foreign"—in Minnesota, in 1910 and 1920, the relation between the death-rates of native-born of the first generation and of foreign-born had been the reverse of what we found it to be in New York.

Occurrence of *Leptospira Icterohemorrhagiæ* in Wild Rats of Baltimore.—ROBINSON (*Am. Jour. Hyg.*, 1924, 4, 327) noted that the animals bearing traumatic scars were most likely to be infected. Therefore, he states it is possible that wild rats are normally infected through abrasions of the skin. While the number of examinations made is not large enough to establish generalities, yet the results tend to show that about 7 per cent of the wild rats of Baltimore are infected with *Lepto-*

spira icterohemorrhagiæ. Dark-field examination of kidney emulsions gives a larger percentage of positive findings than guinea-pig inoculation. Certain strains are without virulence for guinea-pigs. The carrier condition can be produced in white rats, and the leptospiras retain their virulence undiminished after at least four months in the white rat. Carriers are most likely to be large full-grown animals.

The Biseasonal Prevalence of Infantile Paralysis (Acute Anterior Poliomyelitis).—AYCOCK and EATON (*Am. Jour. Hyg.*, 1924, 4, 364) studied the seasonal prevalence of infantile paralysis in the United States over a period of eleven years (1912–1922). They found a marked regularity in the summer prevalence of the disease. A definite secondary increase in its occurrence, usually in March or April, has been established. The authors state that this increase occurs with fair regularity from year to year, and with a certain degree of uniformity in all parts of the country. This suggests the possibility of two modes of transmission of infantile paralysis.

The Relations between a Carnivorous Diet and Mammalian Infections with Intestinal Protozoa.—HEGNER (*Am. Jour. Hyg.*, 1924, 4, 393) states that three rats that were fed throughout their lives (one hundred and seventy-four days) on a carnivorous diet were found to be free from *Giardia muris* and *Trichomonas muris*. Two of these rats contained a few specimens of *Hexamitus muris*. A review of the literature of protozoölogy reveals the fact that intestinal protozoa (amœbæ ciliates and flagellates) have not been reported from carnivorous mammals in nature except very rarely. Examinations were made of fecal specimens, at intervals during a period of seventeen days, from twelve carnivorous animals belonging to ten species (lion, tiger, polar bear, grizzly bear, black bear, Syrian bear, gray wolf, gray fox, red fox, wild cat). No protozoa of any kind were discovered except *Giardia* cysts in the wild cat. Data from the various sources seem to prove that a carnivorous diet is unfavorable for the intestinal protozoa of mammals.

The Protection of Dogs against Rabies by Umeno's Method of Preventive Inoculation.—HATA (*Jour. Immunol.*, 1924, 9, 89) presents the results of 104,629 preventive inoculations of dogs against rabies in Tokio and Yokohama and their environs during the period since the adoption of Umeno's prophylactic method. Only 41 of the inoculated dogs developed rabies, while 1699 of the uninoculated group contracted the disease, notwithstanding the latter group represented only one-third of the total number of dogs in the two prefectures.

Notice to Contributors.—All communications intended for insertion in the Original Department of this JOURNAL are received only with the distinct understanding that they are contributed exclusively to this JOURNAL.

Contributions from abroad written in a foreign language, if on examination they are found desirable for this JOURNAL, will be translated at its expense.

A limited number of reprints in pamphlet form, if desired, will be furnished to authors, providing the request for them be written on the manuscript.

All communications should be addressed to—

DR. JOHN H. MUSSER, JR., 262 S. 21st Street, Philadelphia, Pa., U. S. A.

INDEX.

A

- ABSCCESS, pulmonary, etiology and treatment of, 446, 447
 Actinomycosis, 607
 Alexander, J., surgery of pulmonary tuberculosis, 1, 268, 412, 574
 Alkali in dye therapy, 98
 Allergic phenomena, 611
 Appendectomies at the Lankenau Hospital, 608
 Appendicitis, chronic, 807
 in children, 295, 302, 918
 two hundred and sixty-two consecutive cases of, 608
 Anemia, Addison's, 137
 splenic, 836
 Aneurysm, mycotic, gonococcal and pneumococcal in origin, 381
 of the thoracic aorta, 654
 Angina pectoris, 786
 Ankle-joint, fractures of, 607
 Anopheles, observations on, 156
 Antidote for arsenic, bismuth and mercury poisoning, 764
 Antimony compounds for intravenous use, 728
 Antiseptic, efficient intestinal, 450
 Arsphenamin death, 142
 resistant syphilis, 921
 solutions, viscosity and toxicity of, 311
 Arterial occlusion, coronary, 181
 Arthritis deformans, sulphur in treatment of, 77
 Aschner, P. W., experimental biliary drainage in the dog, 749
 pressure factors in the biliary-duct system of the dog, 812
 Asthma, treatment of, 297, 448
 Atropin, some cardiac effects of, 641
 Auricular flutter, 893

B

- BACILLUS hystolyticus, recovery of, from human feces, 309
 sporogenes, serological agglutination of, 153
 Bacteria in the lungs of alcoholized mice, 779

- Bacteriological study of extirpated tonsils, 623
 Bartlett, F. H., tuberculosis in infancy, 704
 Bassler, A., observation of fat digestion for clinical study and physiological demonstration, 869
 Begg A. C., insulin in general practice, 902
 Bilharziasis, treatment of, by antimony tartrate, 763
 Biliary drainage in the dog, 749
 Bilirubinemia in patients treated with arsphenamin, 768
 Bi-seasonal prevalence of infantile paralysis, 929
 Blackford, L. M., comparison of blood-platelet count in splenic, arterial and venous blood, 723
 Blood chemistry in pregnancy, 773
 composition and properties of, 511
 corpuseles in the newborn period, 300
 of irradiation, effect on, 215
 platelet count in splenic, arterial and venous blood, 723
 pressure, high, 138
 smears in the diagnosis of pertussis, 453
 transfusion, 298, 534
 Boardman, W. W., phenoltetrachlorophthalein in the study of liver function, 688
 Bone marrow and spleen in the treatment of anemia, 819
 Botulinus toxin, digestive juices on the potency of, 927
 studies on, 463
 Boyd, Linn J., aneurysm of the thoracic aorta, 654
 Breast, tumors of the, 799
 Brown, G. E., coronary sclerosis, 165
 Bulmer, F. M. R., some cardiac effects of atropin, 641
 Burke, V., value of alkali in dye therapy, 98

C

- CANCER of the cervix, 618
 high voltage roentgen therapy of, 775

Carbuncle and its treatment by magnesium sulphate, 764
 Carcinoma of the liver, primary, 241
 Cardiopathies, nasal accessory sinuses in, 910
 Carnivorous diet and mammalian infections with intestinal protozoa, 929
 Catalytic action of copper in the destruction of antiscorbutic vitamin in milk, 778
 Cervical cancer, operative results in, 924
 Cesarean section for occlusion of the vagina and calculus, 922
 Children, diseases of the blood in, 917
 intestinal obstruction in, 766
 Cholelithiasis, studies in, 66
 Circulation, the renal, 134
 Clark, W. E., splenic anemia, 836
 Clarke, N. E., a comparative study in digifolin administration, 201
 Clawson, B. J., myocardium in non-infectious myocardial failure, 648
 Cod-liver oil in development of rickets in the breast-fed, 917
 Constipation of civilization, 914
 Contraception, 456
 Coryza, human inoculations with filtered nasal secretions from, 467
 Crile, G. W., endocrinology from the point of view of the surgeon, 625

D

DEATH, a new vascular sign of, 893
 Deaths among taxpayers and non-taxpayers of income tax, Providence, 1865, 776
 Dermatoses due to cosmetics, 767
 Dermatoses, familial, 143
 Diabetes mellitus, cause of death in, 313
 surgery, 495
 Diagnosis, difficult, during pregnancy, 455
 Diaphragm, eventration of, 445
 Dick test in normal individuals and in acute and convalescent cases of scarlet fever, 461
 Digifolin administration, a comparative study in, 201
 Digitalis in certain types of cardiac insufficiency, 914
 therapeutic use of, 762
 Diphtheria, effect of freezing on toxin-antitoxin mixtures, 301
 myocardial lesions of, 624
 Diseases of infancy and childhood, relation of heredity to, 299
 Dislocation, congenital, 446
 Dog, biliary-duct system of the, 812
 Dogs, protection of, against rabies by Umeno's method of preventive inoculation, 929

Drainage of the perivesical region, 447
 Drug addiction in the United States, 131
 Duodenal drainage, rational use of, 761
 Duodenum, stenosis of the, 913

E

Eck, C. P., use of tryparsamide in neurosyphilis, 157
 Empyema, acute, 296
 in children, mortality from, 912
 Encephalitis in children, 765
 Endocarditis, valvular and mural, 292
 Endocrinology from the point of view of the surgeon, 625
 Enteric infections, cutaneous hypersensitiveness in, 131
 Epididymitis, epididymotomy for, 447
 Epilepsy, idiopathic, 635
 Erdmann, J. F., tumors of the breast, 799
 Evans, J. S., bone-marrow and spleen in the treatment of anemia, 819
 Exsanguination-transfusion, 909
 Ex-service man and his lungs, 910

F

FACE, malignant growths about the, 295
 Fat digestion for clinical study and physiological demonstration, 869
 Femoral hernial sac, etiology of the, 913
 Fitz, R., cause of death in diabetes mellitus, 313
 Flat foot, mechanism of the normal and of the, 134
 Fleisher, M. S., relation of Fungi imperfecti to diarrheal conditions, 371
 Foot-and-mouth disease, cause of, 777
 Fracture of the anterior-superior spine of the ilium, 296
 occurring in civil life, 294
 Fried, B. M., primary carcinoma of the liver 241
 Fried, H., primary cancer of the liver, 875
 Friedenwald, J., primary cancer of the liver, 875
 Fungi imperfecti, relation of to diarrheal conditions, 371

G

GALL-BLADDER, infection of, in relation to pernicious anemia, 469
 pathology, 608
 Gall stones in women, 446
 Garvey, J. L., sclerosis of the spinal cord and carcinoma of the stomach, 847

Gastric ulcer, 137
 Gastroenterostomy, unabsorbable sutures in, 913
 Gibson, C. L., chronic appendicitis, 807
 Gilliam operation, 620
 Goiter, 445
 action of iodid in, 297
 effect of iodine in, 909
 Gold-sol reaction, 618
 Goldstein, I., the human dying heart, 388
 Gonorrhea in the female, treatment of
 chronic, 776
 in women, 305
 Gonorrheal complement-fixation test in women, 149
 Gordinier, H. C., coronary arterial occlusion, 181
 Grafts, testicular, 447
 Gram, H. C., composition and physical properties of the normal human blood, 511
 Gray, H., lipoids in 1000 diabetic bloods, 35
 Grieve, I., value of alkali in dye therapy, 98
 Guinea-pigs, tuberculous, 546

H

HAMMAN, L., angina pectoris, prognosis of, 786
 Heart disease, 781
 deaths and disabilities from, 779
 disturbance of, produced by pregnancy, 457
 Hematological responses to injections of streptococci, 115
 Hematuria, significance of, 924
 Hepatitis, 609
 Herpes zoster in Hodgkin's disease, 326
 etiology of, 616
 Hexamethylene dermatitis in the rubber industry, 768
 Hinton, J. W., exophthalmic goiter, 629
 Hodgkin's disease, herpes zoster in, 326
 Holloway, J. K., comparison of blood-platelet count in splenic, arterial and venous blood, 723
 Hookworm disease, control of, 311
 larvæ, notes on the longevity and infectivity of, 467
 Horgan, E., splenic anemia, 836
 Human dying heart, 388
 hypersensitiveness, 312
 Hydrops gravidarum, 145
 Hypertension, problems in, 668
 Hysterectomy as operation of choice, 460

I

INFANCY, wasting disorders of, 301
 Influenza, cause of, 311

Inhibition of spreaders and differentiation of *B. coli* and *B. aerogenes*, 307
 Insulin-like material in the tissues of the normal and diabetic animal, 606
 treatment of diabetes, 609
 Intestines, biliary exclusion from, 911

J

JAUNDICE in eclamptic cases, 146
 problems of, and their significance in surgery, 135
 Joint tuberculosis, treatment of bone and, 912
 Jones, N. W., infection of gall-bladder in relation to pernicious anemia, 469
 Joyce, T. M., infection of the gall-bladder in relation to pernicious anemia, 469
 Julianelle, L. A., hematological responses to injections of streptococci, 115

K

KAHN, M. H., the human dying heart, 388
 a new vascular sign of death, 890
 Kahn reaction in syphilis, 446
 Keratosis blennorrhagica from roentgenotherapy, 618
 Key, J. A., low back pain, as seen in an orthopedic clinic, 526
 Kidney changes in pyloric obstruction, 926
 Kilduffe, R. A., utilization of leukocyte counts, 502
 Knee-joint, surgery of the, 913

L

LACTIC acid milk as a routine feeding for sick and healthy infants, 918
 Lange gold-chlorid reaction on the cerebral fluid in infants and young children, 764
 Larrabee, R. C., splenectomy, its end-results and clinical indications, 47
 Lead in the organism, 779
 Leake, C. D., bone marrow and spleen in the treatment of anemia, 819
 Leighton, W. E., treatment of tetanus, 852
 Leptospira icterohemorrhagiae in wild rats of Baltimore, 928
 Leukemia, a study of mixed, 291
 Leukocyte counts, utilization of, 502
 Life tables for the population of New York State according to nativity, 928
 Lipoids in diabetic bloods, 35
 Liver, primary cancer of the, 875

- Lobar pneumonia, 293
 Loevenhart, A. S., use of tryparsamide in neurosyphilis, 157
 Loose bodies arising from articular surface of the joint, 134
 Lorenz, W. F., use of tryparsamide in neurosyphilis, 157
 Lungs, vital capacity of, 606
 Lutz, J. R., observation of fat digestion for clinical study and physiological demonstration, 869
 Lyter, J. C., pathways of the mediastinum, the lungs and the pleuræ, 882

M

- McLESTER, tachycardias, prognosis of the, 795
 McMillan, T. M., auricular flutter, 893
 Malaria, effect of, on the nervous system, 334
 Malnourished infants, with a note on the use of insulin, 766
 Masson, C. B., effect of malaria on the nervous system, 334
 Maternity work among soldiers' wives, 771
 Mediastinum, lungs and pleuræ, 882
 Meningitis, 142
 Mercurochrome, intravenous use of, 916
 ointment in vaginitis, 621
 Mesothelium, morphology of the peritoneal, 135
 Metabolism of some mineral constituents of cow's milk and of breast milk in the same infant, 452
 Mice, resistance of, to transplanted cancer, 780
 Miller, J. L., evidence that idiopathic epilepsy is a sensitization disease, 641
 Minot, G. R., effect on the blood of irradiation, 215
 Mitral stenosis, congenital, 140
 Moehlig, R. C., action of suprarenal cortex secretion on mesothelial tissues, 553
 Moolten, R. R., non-calculous gall-bladder, 684
 Mucous colic, so-called, 612
 Murphy, W. P., cause of death in diabetes mellitus, 313
 Myocardium in non-infectious myocardial failure, 648
 Myomectomy, indications for, 148

N

- NASOPHARYNX, absorption of substances, from, 293
 Neuhof, S., problems in hypertension, 668

- Neurosyphilis, use of tryparsamide in, 157
 Newborn, intracranial hemorrhage in, 767
 natural immunization in, 769
 thymus of, 612
 Norris, G. W., heart disease, prognosis in organic, 781

O

- OBESITY and its treatment, 299
 Otitis media, 614
 Ovary, hypernephroma of, 139

P

- PAIN as seen in an orthopedic clinic, 526
 Pancoast, H. K., herpes zoster in Hodgkin's disease, 326
 Pancreatitis, acute, 762
 Paratyphoid-enteritidis group, 156
 Patients in private practice and the physician's responsibility, 771
 Pellagra, treatment and prevention of, 311
 Pelouze, P. S., behavior of tuberculous guinea-pigs under parathyroid and calcium administration, 546
 Pemphigus, chlorid retention in, 769
 Pendergrass, E. P., herpes zoster in Hodgkin's disease, 326
 Penetration of normal mucous membranes of the rabbit by treponema pallidum, 466
 Peritonitis, primary pneumococcal, 132
 Pertussis, diagnosis of, 453
 treatment of, by the roentgen-ray, 141
 Phenoltetrachlorophthalein in the study of liver function, 688
 Physostigmin and pituitrin, action of, 136
 Pleurodynia, or "Devil's grip," 564
 Pneumococcus, soluble specific substance of, 778
 Pneumonia, treatment of, 915
 Poliomyelitis, an immunizing strain of the virus of, 310
 Postencephalic behavior disturbances without physical signs, 451
 Postmature child, 147
 Pregnancy, pyelitis of, 454
 in scurvy in guinea-pigs, 765
 severe disturbance of the heart produced by, 457
 toxemias of, 605
 Pucher, G. W., sulphur in treatment of arthritis deformans, 77
 Purified Dick scarlatinal toxin, properties of, 926
 Pyelitis of pregnancy, 454

R

- RADIUM in treatment of tonsils, 18
 Ragweed pollen, 309
 Randall, A., antimony compounds for intravenous use, 728
 Raw-fruit cure, 612
 Rectal digital therapy, 291
 surgery, 294
 Reeves, W. P., splenic anemia, 836
 Reifenstein, B. W., mycotic aneurysm, gonococcal and pneumococcal in origin, 381
 Reimann, H. A., sulphur in treatment of arthritis deformans, 77
 Reitz, T. F., use of tryparsamide in neurosyphilis, 151
 Reviews—

- Andrews, Bulloch, Douglas, Dreyer, Gardner, Hildes, Ledingham and Wolf, Diphtheria, 285
 Artschwager and Smiley, Dictionary of Botanical Equivalents, 286
 Bacon, Obstetrical Nursing, 597
 Bandler, Medical Gynecology, 758
 Bayly, Venereal Disease, 597
 Beck, Diseases of Nose, Throat and Ear, 287
 Bickham, Operative Surgery, 440
 Bryce, T. H., Ouan's Elements of Anatomy, 438
 Buerger, Circulatory Disturbances of the Extremities, 289
 Bulletin No. X of the International Association of Medical Museum, 290
 Burger, Pathologisch-Physiologische Propädeutik, 287
 Bosanquet and Wilson, Pathology and Morbid Anatomy, 126
 Cabot, Differential Diagnosis, Vol. II, 285
 Campbell, Rommel and Hoffman, Modern Treatment and Medical Formulary, 759
 Clendening, Modern Methods of Treatment, 905
 Collected Papers of the Mayo Clinic and the Mayo Foundation, 443
 Cotton, Dislocations and Joint Fractures, 439
 Cowdry, General Cytology, 906
 Craig, Diseases of Middle Life, 757
 Cushny, Pharmacology and Therapeutics, 437
 Dally, High Blood-pressure, 128
 Danielopolu, L'Angine de Poirine, 598
 De Lee, Principles and Practice of Obstetrics, 758
 Diepgen, Geschichte, 130
 Douglas and Priestley, Human Physiology, 600

Reviews—

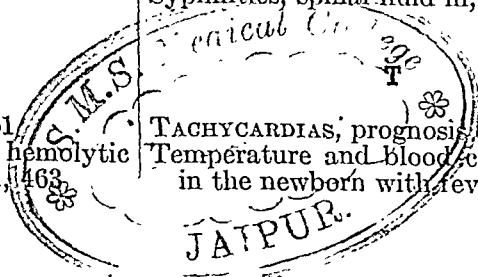
- Du Bois, Basal Metabolism in Health and Disease, 752
 Edgell, Theories of Memory, 442
 Elias, Jagie and Luger, Bedside Examination, 128
 England, First Century of the Philadelphia College of Pharmacy and Science, 902
 Faust, Studies on Schistosomiasis Japonica, 439
 Fox, Outlines of Medical Hydrology, 288
 Fox and Penrose, Disease in Captive Wild Animals and Birds, 754
 Gardiner, Handbook of Skin Diseases, 902
 Handbook for Mental Nurses, 128
 Harrop, Management of Diabetes, 288
 Hermann, Methods in Medicine, 129
 Hoffstätter, Die Rauchende Frau, 759
 Holmes, Louis Pasteur, 288
 Hornibrook, Culture of the Album, 442
 Horowitz, Diabetes, 290
 International Medical Annual, 437
 Joslin, Diabetic Manual, 284
 Kantor Disorders of Digestion, 759
 King, Basal Metabolism, 753
 Lillie, Protoplasmic Action and Nervous Action, 908
 Lindsey, Medical Quotations from English Prose, 753
 Luke, Anesthesia in Dental Surgery, 908
 McFarland, Surgical Pathology, 603
 Mallory and Wright, Pathological Technic, 441
 Marlow, Relative Position of Rest of the Eyes and the Prolonged Occlusion Test, 443
 Martin, Artificial Limbs, 906
 May, Diseases of the Eye, 907
 Medical Department of the United States Army in the World War, 903
 Montague and Stewart, Pruritus of the Perineum, 127
 Moodie, Paleopathology, 444
 Morley, Hemorrhoids, 289
 Newmayer, Inspection of the Schools for the Health Officer, 284
 Norris and Landis, Diseases of the Chest, 438
 Ophthalmic Year Book, 1923, Vol. XIX, 129
 Pardee, Clinical Aspects of the Electrocardiogram, 907
 Petty, Diabetes, 757

Reviews—

- Poole, *The Avalanche*, 752
 Porter, *Management of the Sick Infant*, 598
Practical Medicine Series, Vol. I, 129
 Price, *Hygiene and Public Health*, 437
Radium Report of the Memorial Hospital, New York, 442
 Reynolds and Macomber, *Fertility and Sterility in Human Marriages*, 599
 Rossiter, *Romance of a Living Temple*, 905
 Rudolf, *Medical Treatment of Disease*, 602
 de Schweinitz, *Diseases of the Eye*, 601
 Sharp, *Foundation of Health*, 903
 Sharpey-Schaffer, *The Endocrine Organs, Part I*, 286
 Simon and Base, *Manual of Chemistry*, 126
 Smith, *Essays on the Evolution of Man*, 601
 Thewlis, *Geriatrics*, 130
 Thomson, *Tuberculosis of the Larynx*, 285
 Thorek, *Human Testis and Its Diseases*, 904
 Tocher, *Record of Measurements, Weights and Other Facts Relating to Man*, 904
 Turner, *Diseases of Nose, Throat and Ear*, 598
 Walters, *Domiciliary Treatment of Pulmonary Tuberculosis*, 602
 Weil, *The Internal Secretions*, 599
 Whiting, *Aids to Medical Diagnosis*, 290
 Whitla, *Dictionary of Treatment*, 760
 Rheumatic fever, pathogenesis of, 463
 Roentgen-ray intoxication, 133
 studies of stomach function, 615
 rays, measurement of the pelvis by, 458
 therapy of benign uterine bleeding, 306
 Rosenberger, R. C., behavior of tuberculous guinea-pigs under parathyroid and calcium administration, 546
 Rothschild, M. A., studies in cholelithiasis, 66
 Rudolf, R. D., some cardiac effects of atropin, 641
 Scarlet fever, study of hemolytic streptococci associated with, 153
 School children, mental health problems in, 915
 Schoonmaker, G. D., phenoltetrachlorophthalein in the study of liver function, 688
 Sclerosis, coronary, 165
 spinal cord and carcinoma of the stomach, 847
 Seelig, M. G., diabetes surgery, 495
 Serum tetrachlorophthalein test for liver function, 606
 Sheppard-Towner act, 922
 Silver arsphenamin, action of, 769
 Sleep, loss of, effect on composition of blood and urine, 151
 Small, J. C., protozoan organism within erythrocytes of patients suffering from pleurodynia, 570
 Smith, C., treatment of tetanus, 852
 Sodium citrate, effects of injection of, upon bleeding, 607
 Splenectomy, 47
 Spondylolisthesis, 295
 Sporotrichosis in the rat, 144
 Spotted fever, immunity in Rocky Mountain, 780
 Spurling, R. G., effect on the blood of irradiation, 215
 Stenosis, pyloric, in infants, 296
 Stern, L. D., sclerosis of the spinal cord and carcinoma of the stomach, 847
 Stetson, R. E., blood transfusion, 534
 Streptococcus hemolyticus in scarlet fever, 308
 Stricture of female urethra, 150
 Sulpharsphenamin in Vincent's angina and stomatitis in children, 450
 Sulphemoglobinemia, 89
 Sulphur in treatment of arthritis deformans, 77
 Suprarenal cortex, action of, on mesothelial tissues, 553
 Suprarenin in clinic and practice, 298
 Sweeney, J. A., auricular flutter, 893
 Syphilis as a complication of pregnancy in the negro, 770
 congenital, results in treatment of, 614, 777
 diagnosis and treatment of, 136
 as a factor in the etiology of mental deficiency, 465
 from an experimental point of view, 919
 primary and secondary, 697
 treatment, results in, 921
 Syphilitics, spinal fluid in, 144
 TACHYCARDIAS; prognosis of the, 795
 Temperature and blood concentration in the newborn with fever, 453

S

SCARLET FEVER antitoxin, 461
 culture filtrates of hemolytic streptococci from, 463



- Tendon of Achilles, tenotomy of the, 912
- Tetanus, treatment of, 852
- Thomas, B. A., primary and secondary syphilis, 697
- Thyroidectomized sheep, pathological changes in, 927
- Thyroid treatment of the nephroses, 611
- Tonsillectomy, effect of, on the general health, 451, 605
- Torrey, R. G., epidemic diaphragmatic pleurodynia, or "Devil's grip," 564
- Toxemia of pregnancy, 302, 605
 cerebral symptoms produced by, 304
 treatment of, 613
- Tuberculosis in infancy, 704
 pulmonary, 1
 studies on the relation of mineral dusts to, 154
 surgery of pulmonary, 268, 412, 574
- Tumor susceptibility and heredity, 467
- Typhoid fever and ice, 779
 saline vaccine, 151
- U**
- ULCER, duodenal, among medical men, 135
- Ultraviolet light, skin resistance to, 617
- Ureteral catheterization, 623
- Urinary bladder, reactions of, in canine anaphylaxis, 308
- Use of diphtheria antitoxin, 467
- Uterine fibroids, surgical treatment of, 774
 treatment of, 925
 prolapse, operation for, 150
 operative treatment of, 459
 secretion, nature of, 619
 treatment of, 622
- V**
- VACCINATIONS, protection against typhoid-like, by, 152
- Venereal disease, relation of, to child-birth, 923
- Venous pressure, 761
- Vesical distention, 133
- Virus of poliomyelitis, activity of, 466
- Vitamin C, lack of, on resistance of the guinea-pig of bacterial infection, 465
- Vogel, K., sulphemoglobinemia, 89
- W**
- WACHOWIAK, M., relation of Fungi imperfecti to diarrheal conditions, 371
- Wilensky, A. O., studies in cholelithiasis, 66
- Williams, F. H., radium radiations in treatment of tonsils, 18
- Willius, F. A., coronary sclerosis, 165
- Wilson's disease in infancy, 140
- Winkelstein, A., pressure factors in the biliary duct-system of the dog, 812
- Woolstein, M., tuberculosis in infancy, 704

